E. I GRIN

EPIDEMIOLOGY AND CONTROL OF ENDEMIC SYPHILIS

Report on a Mass-Treatment Campaign in Bosnia

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The work of the Organization is carried out by three organs the World Health Assembly the supreme authority to which all Member States send delegates the Executive Board the executive organ of the Health Assembly consisting of 18 persons designated by as many Member States and a Secretariat under the Director-General

The scope of WHO s interests and activities exceeds that of any previous international health organization and includes programmes relating to a wide variety of public-health questions malaria tuberculosis, venereal diseases, other communicable diseases maternal and child health mental health social and occupational health nutrition nursing environmental sanitation, public-health administration professional education and training and health education of the public. In addition WHO undertakes or participates in certain technical work of international significance such as the compilation of an international pharmacopoeia the setting-up of biological standards and of standards for insecticides and insecticide-spraying equipment, the control of addiction-producing drugs, the exchange of scientific information the drawing-up of international sanitary regulations the revision of the international list of diseases and causes of death the collection and dissemination of epidemiological information, and statistical studies on morbidity and mortality

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Report on a Mass-Treatment Campaign in Bosnia

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CONTENTS

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FOREWORD

Success in the prevention and control of any disease depends on a knowledge of its natural history. It is not sufficient to study the course of the disease and its behaviour in the individual; the investigations must be carried out among the affected population as a whole, and particularly into their environment. The characteristics, habits, and customs of man in his physical, mental, social, and economic surroundings must be considered if the underlying causes of mass disease are to be understood. With communicable diseases, the relationship between host and environment, as well as between parasite and host, must be defined so that epidemiology becomes broad method by which the natural history of the disease is elucidated, leading to a better understanding of the nature, sources, means of spread, and eventual control of the disease.

The present work is an attempt to study the natural history of syphilis in Bosnia in this broader sense. The Bosnia syphilis is a treponemal disease, usually non-venereally acquired in childhood, which has been known to be endemic in the region for many centuries as result of the invasion of Europe in the 17th and 18th centuries by the Ottoman armies. Many pockets of land populated by people of Turkish origin were left behind in eastern Europe, in which the disease has remained very prevalent until recent times. Bosnia is the largest of those areas where the social and economic conditions, associated with very low standards of hygiene and of living in general, have for centuries maintained an environment favourable to repeated exposures to and the transmission of *Treponema pallidum* by direct and indirect contact—domestic utensils, etc. This epidemiological setting has persisted until the present day and is similar to that which existed in Cromwellian England when the *Sibbens* was a widespread non-venereally acquired syphilitic infection in children. The same applies to the *Radesyge* in 16th-century Norway and to other non-venereal treponemal infections in children found in different countries of Europe in the 18th and 19th centuries.

The natural course of syphilis acquired in childhood, including its epidemiological, clinical, laboratory and other aspects, has not been adequately described in existing literature. The present study represents an important contribution to the limited knowledge on the subject. The environmental factors and their influence on the perpetuation of the infection as an endemic disease, the course of the disease over decades, and present control efforts are discussed, facts about this endemic type of syphilis are appraised and original theories and new considerations are advanced explaining its behaviour in primitive environment.

This monograph, therefore, is not only of interest from the point of view of epidemiology and the successful control of non-venereal syphilis problem in rural areas, and because it fills important gaps in medical knowledge, but should also be of considerable value in the control of other treponematoses, such as bejel, njovera and particularly yaws, all of which have epidemiological features similar to those of endemic syphilis and in which only the resulting clinical syndromes are different. Furthermore, this study has contributed to the drawing-up of plans for both special and general public-health measures in the areas under consideration. A treponematosis-control programme is already in operation, and it is presumed that the relationship already established with the people and the new record system will contribute to the improvement of local health measures.

This study is the first of series on treponematoses, prepared under the auspices of the World Health Organization. Ed.

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CHAPTER 1

INTRODUCTORY REMARKS ON BOSNIA-HERZEGOVINA

The People s Republic of Bosnia and Herzegovina occupies a central geographical position among the Federal Republics of Yugoslavia. It is the third largest, with an area of 51,567 km² or 20.7 % of the Yugoslav territory It consists of two geographical units, Bosnia occupying the northern and central part and Herzegovina the southern. It is predominantly mountainous, 66% of its territory consisting of mountains and highlands with a total wooded area of 2,134 196 hectares.

At the frontier of Bosnia and Herzegovina the temperate continental climate meets the Mediterranean climate. Central and eastern Bosnia have a typical Central European climate with cold snowy winters and moderately warm summers. Favourable natural conditions for growing cereals and fruit trees, particularly plum trees, ample resources in minerals and ores, extensive forests, and rich reserves of water-power give an excellent basis for the rapidly developing industrialization of the country

On account of the favourable natural conditions, the present territory of Bosnia-Herzegovina was settled as long ago as the remotest prehistoric times, the chief representatives of its ancient civilization being the Illyrians. They were subjugated at the beginning of the 1st century A.D. by the Romans, who ruled these regions for more than four centuries. After the splitting-up of the Roman Empire into the Eastern and Western Empires, the area occupied became the theatre of conflicts between Eastern and Western civilization. The first Slavs started to invade Bosnia at the beginning of the 7th century and in the valley of the river Bosna they formed the core of a mediaeval State.

During the course of history nearly all its present provinces became attached to Bosnia, and its boundaries corresponded more or less to the present frontiers. Meanwhile, the State was not particularly strongly organized, and Bosnia came under Turkish rule at the beginning of the 15th century without much resistance. Thus, it came to occupy a strategic position between East and West.

Turkish rule in Bosnia-Herzegovina made a deep and lasting impression on social, economic, and cultural life, and the influence of Islamic civilization became predominant. The Mohammedanized population, though it had broken off almost all contact with its national traditions, still retained the language and some customs as its specific national mark. Meanwhile, the rural districts experienced cultural and economic stagnation, and the standard of life remained extremely primitive.

Since 1948, the Yugoslav health administration has developed a nationwide syphilis-control programme as part of its general health activities. In Bosnia, a special effort has been made to control endemic syphilis as part of the general programme for social and economic development. The World Health Organization (WHO) and the United Nations International Children's Emergency Fund (UNICEF) have participated in the programme at the request of the Yugoslav Government. International interest in the endemic syphilis in Bosnia, however is not of recent date. In 1933-6, the Rockefeller Foundation supported national field studies into the nature of the disease with a view to defining the differences that were believed to exist between the endemic type of syphilis found in Bosnia and the sporadic venereal syphilis found in other parts of the world. With the increase of co-operation among nations in matters of health after the second World War and, on the technical side, after the introduction of repository penicillin preparations, it became possible to approach this problem on a large scale and in a more practical manner A wide case-finding and treatment programme has been in operation in Bosnia since 1948, and it has attracted particular international attention as one of the first systematic programmes in the world aimed at eliminating an endemic infectious disease through mass treatment.

Preliminary discussions between the Yugoslav health administration and WHO which took place in 1947 and were followed by a field study by Dr T Guthe, of WHO, and Dr D Borenstein, of UNICEF led to the formulation of plans for the current programme against endemic syphilis in Bosnia as part of the nationwide syphilis-control programme. Various supplies and equipment were furnished by UNICEF and several WHO expert consultants and advisers have subsequently studied the Bosnian programme in its different phases of development, among them Dr Evan W Thomas, Professor of Clinical Medicine, New York University and Dr E. Gurney Clark, Professor of Epidemiology Columbia University in 1950 and 1951 The planning, implementation, and follow-up of the programme have been the responsibility of the Yugoslav health administration and of the Field Director Dr E. I. Grin, Director of Health, Sarajevo, the author of the present paper

As a complement to this study Dr T B. Turner and Dr D. H. Hollander of the International Treponematosis Laboratory Center submitted a contribution—published as an annex—on two strains of *Treponema pallidum* isolated from two Bosnian patients.

At the request of the author Dr E G Clark undertook to comment on and discuss various aspects of the mass campaign. His views were embodied in a paper presented to the fourth session of the WHO Expert Committee on Venereal Infections and Treponematoses, which met in London from 28 July to 2 August 1952. This paper will be included in the report of the Expert Committee, which will be published in the *World Health Organization Technical Report Series* subject to approval by the Executive Board.

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groups are very intermingled, and it is impossible to draw ethnical frontiers. The problem represented by the Moslem population is being solved by encouraging their cultural, educational, and social development in order to bring them more speedily to a stage where they will realize that they belong to either the Serbian or the Croatian ethnical group.

According to the census of 15 March 1948, the most important social groups were as follows peasants, 1,966,406 industrial workers, 291 408 civil servants, 185,525 craftsmen, 31,261 and tradesmen, 12,913 In the present period of social and economic reorganization of the industrial structure, a continuous change is taking place in the social composition of the population, which is increasing rapidly in towns and industrial centres. The population of Sarajevo, for instance, increased by 57 6% between the liberation and 1948.

There are no big cities in the People s Republic of Bosnia and Herzegovina but, as in other Balkan countries, there are numerous small towns and villages, Sarajevo is the industrial, political, cultural, and communications centre of the Republic. Its cultural importance has increased considerably since the foundation of the University there in 1949

Turkish rule lasted until 1878 when the Congress of Berlin gave Austria Hungary a mandate to enter Bosnia. The Austrian occupation of Bosnia-Herzegovina, with its semi-colonial methods of administration, provoked a strong national movement resulting in the assassination at Sarajevo in 1914 of the heir to the Austrian throne, the Archduke Ferdinand.

In 1918 after the first World War the newly created State of Serbs, Croats, and Slovenes brought about no essential social or economic changes in Bosnia Herzegovina, and the much-hoped-for cultural and industrial development made but very slow progress. Bosnia Herzegovina remained, in fact, only a sphere of interest in a common State, while religious and national differences became more and more acute.

At the beginning of the second World War when the occupation was followed in this part of Europe as in others by a struggle for national liberation, which started on 27 July 1941 the crisis threatening social, national and political disintegration and economic stagnation was surmounted. By paying a huge toll in human life (the war claimed 700 000 victims in Bosnia-Herzegovina alone) in suffering, and in material losses, the Federal People's Republic of Yugoslavia was created. The People's Republic of Bosnia and Herzegovina is recognized under the Yugoslav Constitution as a member of the Federal Republic with equal rights.

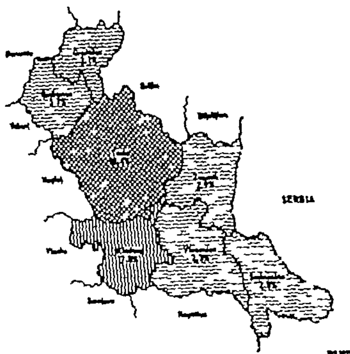
The low cultural standard prevalent in Bosnia Herzegovina during its historical evolution is best illustrated by the high illiteracy rate. The Austro-Hungarian occupation found a population more than 95% illiterate, but compulsory primary-school education was introduced only in 1911 Actually not more than about 15% of school-age children went to primary schools, and Moslem girls did not go to school at all. Owing to these facts, there was no real progress in the cultural life of the population.

After the first World War the population of Bosnia Herzegovina was still about 87% illiterate among the Moslem women, who had almost no rights and who lived in complete subjection to the men only 1 in 1 000 was literate. As late as 1939 56.4% of the men and 87.6% of the women in Bosnia-Herzegovina were still illiterate. After the liberation, rapid progress took place, and between then and the end of the scholastic year 1949-50, about 600 000 persons had learned to read and write, while the number of primary schools had increased from 1,043 to 1,847

The population of the area is 2,565,277 (1,237,381 male and 1,327,896 female), or 16.3% of the total population of Yugoslavia. The annual population increase is 2.27%, the highest rate among the Yugoslav Republics. The average population-density increased in Bosnia Herzegovina from 45 per km² in 1931 to 49.9 in 1948 The population is denser in the north, where cereals grow well, and is less dense in eastern and central Bosnia.

Ethnically the population of Bosnia Herzegovina is almost exclusively Slav being composed of Serbs and Croats. Geographically these two

FIG. 2. INCIDENCE OF ENDEMIC SYPHILIS IN NORTH-EASTERN BOSNIA, 1905-11 (BASED ON CLINICAL SYMPTOMS ONLY)



the period between the first and second World Wars, for example, were useful but lasting results were achieved only in limited areas where the infection-rate was often low or in areas situated near the more important population centres where the programme could be more easily supervised. Limited improvements in living standards and sanitary conditions sometimes took place in such areas, but only *with difficulty* did they reach certain others in the less accessible regions of Bosnia.

The district of Visoko, north of Sarajevo is a good example of an area where a general improvement in social and economic conditions accompanied the development of a syphilis-control programme. During the syphilis survey of 1905-11 8.2% of the population of this district was found to have clinical manifestations of the disease, and 3,251 clinical cases were diagnosed among these were 2,251 cases of early infectious (secondary) syphilis. After the first World War intensified control-work was undertaken, and numerous field facilities were established. In 1936,

were found, 17 746 in the early stages, 6,943 in the tertiary stage, and 33,276 in the latent stage. The infection-rate among the population examined was 11.8%.

As there was no uniformity in the organization of the programme, in the diagnostic procedures used or in the control of infective cases by follow up or analysis of the data collected, the findings were not sufficiently reliable to form a basis for valid conclusions on the true nature and extent of the problem at the time or on the effect of the programme. Nevertheless, the observations made give valuable information on the geographical extent of the disease and confirm that syphilis was endemic, and sometimes epidemic, in many parts of Bosnia.

Finally in 1941 at the beginning of the German occupation, plans were drawn up and an attempt was made to launch a general campaign to eliminate endemic syphilis as a rural health problem in the area. Little progress was made, however and the undertaking was soon abandoned. The situation was aggravated during the war by the migration of large numbers of refugees and by a further deterioration in living conditions and sanitation this gave rise to a number of new endemic foci in towns and rural areas.

Fig. 1 shows the areas of Bosnia and Herzegovina where endemic syphilis was prevalent in 1951

The main reasons for the failure of previous efforts [88] to control syphilis in Bosnia are considered to be the following

1 Action against the disease was not undertaken simultaneously throughout all the infected areas and, in those areas where control efforts were made, there were frequently long interruptions in the work.

2. No systematic examination of the entire infected region was attempted, such work being restricted to small areas only a large number of cases were therefore not discovered, and numerous small and large foci of infection remained.

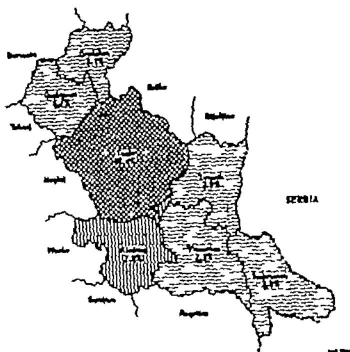
3 Emphasis was placed on the clinical and pathological, rather than on the epidemiological, aspects of the disease.

4 Modern antibiotics were not available and only a small number of infectious cases completed treatment with the classical chemotherapy methods, which were not suitable for mass work in isolated, and sometimes almost inaccessible, rural areas.

5. Low social and economic standards, primitive sanitation, and poor living conditions, remaining almost unchanged, created a favourable epidemiological environment for the recurrence of cases and for the perpetuation of the disease.

It would, however be incorrect to give the impression that the previous efforts to combat syphilis in Bosnia were of no value. The activities in

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(BASED ON CLINICAL SYMPTOMS ONLY)



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when the average infection rate was 18.7 ‰ the great majority of the persons infected had latent syphilis.[36] This programme was continued until the second World War and, during investigations carried out in 1950, nearly half a century after the initiation of control work, the infection-rate was found to be only 3 17 ‰ again with the great majority of the cases in the latent stage.

A similar improvement has been observed in a few other frontier areas but numerous endemic foci remained, particularly in north-eastern Bosnia, where there was no appreciable change until the present large-scale programme (1948-52) described in this paper

Fig. 2, 3 and 4 show the recorded prevalence of endemic syphilis in north-eastern Bosnia before the first World War between the wars, and after the second World War respectively Fig. 4 is based on the systematic survey carried out at the beginning of the present mass campaign.

It is apparent that no marked changes have taken place in the prevalence of syphilis in this area since 1911 Variations in infection-rates are to be

FIG. 3. INCIDENCE OF ENDEMIC SYPHILIS IN NORTH-EASTERN BOSNIA, 1927-33

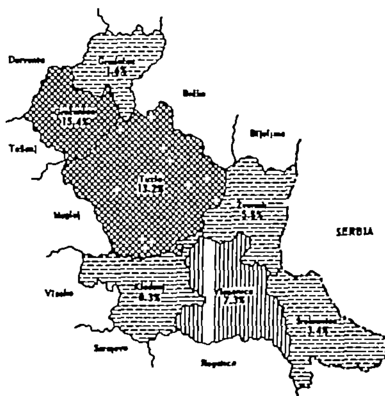
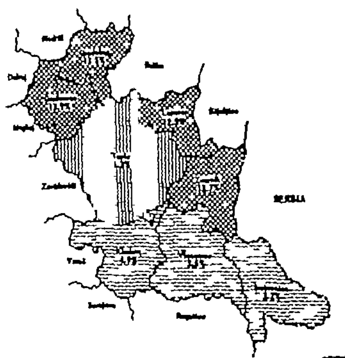


FIG. 4. INCIDENCE OF ENDEMIC SYPHILIS IN NORTH-EASTERN BOSNIA, [illegible]



seen but they may to some extent be attributed to the dissimilarity between the methods used to obtain and record data, to differences in diagnostic methods, and to varying degrees of completeness in the coverage.

CHAPTER 3

THE CONCEPT OF ENDEMIC SYPHILIS

From observations made over the course of years[illegible] and from information gathered during the present syphilis-control campaign in Bosnia,[illegible] it is apparent that the essential characteristics of this treponemal disease are as follows

1 It has, as a rule, a non venereal mode of transmission and is not considered a venereal disease by the infected population it affects both sexes equally at all ages, but is most frequently acquired in childhood.

2 It is prevalent in areas where a low standard of education and poor economic and social conditions, with primitive sanitary and dwelling arrangements, are general these factors make for repeated exposure to treponemes, and the direct and indirect spread of disease is greatly facilitated.

3 Its particular mode of spread, through common domestic and household utensils and other direct and indirect contacts, often results in the appearance of infectious mucous lesions in the oral region as the first symptoms.

4 There are no essential differences in the nature of the symptoms of endemic syphilis and those of sporadic venereal syphilis, the symptomatology of both including cardiovascular and neurological involvement.

It will be seen, therefore, that syphilis in Bosnia must be considered primarily as an epidemiological rather than a clinical problem. The infection became endemic because of the existence over centuries of epidemiological features favouring a certain mode of spread. The term "endemic syphilis" subsequently became associated with non-venereal syphilis, usually acquired in childhood, in which repeated exposure to small numbers of treponemes over a period of time gives rise to the predominance of certain features not usually encountered in environments where venereal transmission makes a different age-group primarily susceptible. Syphilis cannot develop or persist in this endemic form if the various environmental factors referred to above are absent.

Similar considerations are probably applicable to other non-venereally acquired treponemal diseases,[illegible] such as bejel[1,illegible] and "njovera"[illegible] both non-venereal treponemal infections generally encountered in children in Middle Eastern, Asian, and African populations.[illegible]

In the early Bosnian control-programmes, emphasis was placed on the clinical aspects of the disease, and certain erroneous conclusions were drawn, in particular that this infection was a benign illness. This resulted

in insufficient attention being paid to the real nature of the problems and delayed the establishment of realistic public-health measures for the control of the disease. It was not until the beginning of the present campaign that it became evident that the major emphasis had to be placed on the epidemiological aspects if the disease was to be successfully controlled.

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From observations made over the course of years[illegible] and from information gathered during the present syphilis-control campaign in Bosnia,[illegible] it is apparent that the essential characteristics of this treponemal disease are as follows

1 It has, as a rule, a non-venereal mode of transmission and is not considered a venereal disease by the infected population It affects both sexes equally at all ages, but is most frequently acquired in childhood.

2. It is prevalent in areas where a low standard of education and poor economic and social conditions, with primitive sanitary and dwelling arrangements, are general these factors make for repeated exposure to treponemes, and the direct and indirect spread of disease is greatly facilitated.

3 Its particular mode of spread, through common domestic and household utensils and other direct and indirect contacts, often results in the appearance of infectious mucous lesions in the oral region as the first symptoms.

4 There are no essential differences in the nature of the symptoms of endemic syphilis and those of sporadic venereal syphilis, the symptomatology of both including cardiovascular and neurological involvement.

It will be seen, therefore, that syphilis in Bosnia must be considered primarily as an epidemiological rather than a clinical problem. The infection became endemic because of the existence over centuries of epidemiological features favouring a certain mode of spread. The term "endemic syphilis" subsequently became associated with non-venereal syphilis, usually acquired in childhood, in which repeated exposure to small numbers of treponemes over a period of time gives rise to the predominance of certain features not usually encountered in environments where venereal transmission makes a different age-group primarily susceptible. Syphilis cannot develop or persist in this endemic form if the various environmental factors referred to above are absent.

Similar considerations are probably applicable to other non-venereally acquired treponemal diseases,[illegible] such as bejel[1, illegible] and "njovera"[illegible] both non-venereal treponemal infections generally encountered in children in Middle Eastern, Asian, and African populations.[illegible]

In the early Bosnian control-programmes, emphasis was placed on the clinical aspects of the disease, and certain erroneous conclusions were drawn, in particular that this infection was a benign illness. This resulted

in insufficient attention being paid to the real nature of the problem and delayed the establishment of realistic public-health measures for the control of the disease. It was not until the beginning of the present campaign that it became evident that the major emphasis had to be placed on the epidemiological aspects if the disease was to be successfully controlled.

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CHAPTER 4

EPIDEMIOLOGICAL CONSIDERATIONS

In Bosnia, endemic syphilis is mainly found among the rural population, but it is not evenly distributed over the different areas, despite what appear to be identical living conditions. Sometimes one village is heavily infected while a neighbouring one may remain free or have only a few cases infections may be found in one group of houses in a village while other groups remain unaffected. There may be considerable variations in infection rates within one region, and even within smaller communities. For instance, in one district (Zvornik), which includes 16 administrative units, 41 833 persons were systematically examined. The general prevalence was 13 7 %, while the prevalence in the administrative units varied from 5 7 % to 24 8 %.

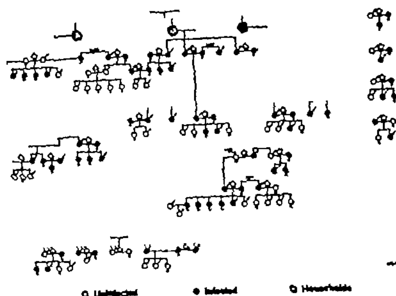
If a comparison is made of the infection-rates in the various villages within one of these units, the variations become even more marked. Thus, in an administrative unit (Sapna), with a general prevalence of 24.8 % the minimum rate was 4.2 % and the maximum, 60.1 %.

It is difficult to explain this uneven distribution of endemic syphilis social and family customs, migratory factors, the topographical structure of the country and poor communications, which hinder easy access to certain places, may be important factors.

A family " map " of the inhabitants in a small village is given in fig. 5 This indicates that close family links, and social contacts, constitute an important factor in facilitating the spread of the disease. This example is taken from investigations in a Moslem village before the second World War although certain social customs no longer exist today for instance, the frequent changes of wives, the findings are still important. The village was founded by three brothers (shown as A, M, and S) all of whom were infected with syphilis. With the arrival of newcomers and intermarriage between the inhabitants of the village and those of neighbouring settlements, the community expanded. At the time of the investigation the village was three generations old and had 25 dwellings with 116 inhabitants (61 male and 55 female) 44 % of the married women and 36.3 % of the married men had been married two or more times. All the families in the village, with the exception of five, were related to one another A high infection-rate (56.1 %) resulted from the close contacts which existed between the households.

As a rule, Bosnian villages are not compact communities with the houses clustering together or semi-detached but are dispersed over quite

FIG. 3. FAMILY DISTRIBUTION OF ENDEMIC SYPHILIS IN A SMALL VILLAGE (BOPOTNIK)



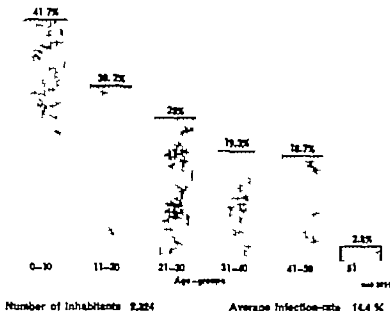
a large area, either individually or in small groups. A study of the prevalence of endemic syphilis in relation to the size of the community reveals that the smaller and more compact the community the higher the infection-rate, since there are more opportunities for the transmission of treponemes. Thus, a survey recently carried out in 322 villages in highly infected areas as part of the present control-programme shows a progressive decrease in the infection-rate as the population increases. Villages with a population of up to 200 had an average infection-rate of 22.5 %, those with from 200 to 400 people, 16.2 %, those with from 400 to 600 people, 12.6 %, and those with over 600 people, only 9.1 %.

FIG. 4. RATE OF INFECTION WITH ENDEMIC SYPHILIS BY AGE-GROUPS IN A FRESH FOCUS (BRIO MACKOVAC)



Fig. 6 shows the absolute distribution of endemic syphilis among age-groups however it will be seen from fig. 7 that there are wide differences in the age-specific infection-rates, the highest rate of secondary syphilis being found in children.

FIG. 7 PROPORTION OF SECONDARY SYPHILIS TO TOTAL ENDEMIC SYPHILIS BY AGE-GROUPS IN A FRESH FOCUS (MINO MACKOVAC)



A similar distribution is found in the case of untreated latent syphilis if quantitative serological reactions are used as an index. This is illustrated in fig. 20, from which it will be seen that the highest age-specific infection-rate of positive serological reactions is found in the age-groups 0-10 and 11 20 Fig. 20 also shows that, if syphilis is allowed to follow its natural course, the higher the age-group, the less frequent the positive serological reaction.

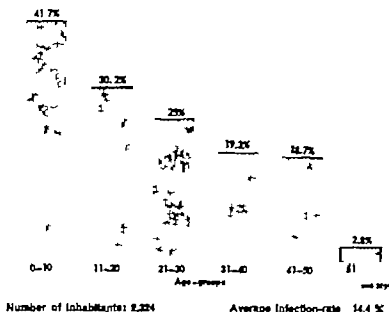
In areas where endemic syphilis is actively spreading, the percentage of children infected is particularly high. On this basis, conclusions can be drawn as to whether the disease is increasing or decreasing in a particular area in other words, wherever a high proportion of infected children is found, syphilis is more active and the endemic spreading, while in places where that proportion is low the disease is less active and the endemic waning. As fresh infections among children become rarer more cases of latent syphilis are found in the higher age-groups, and a larger proportion of the lower age-groups remain uninfected.

The mode of transmission of endemic syphilis in Bosnia is mostly non-venereal in character The rural population does not generally associate the disease with sexual contact, and endemic syphilis does not

FIG. [illegible]. COMMON USE OF THE IBRIK — ONE OF THE MOST FREQUENT METHODS OF SPREAD OF ENDEMIC SYPHILIS

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FIG. 12. MUCOUS PATCHES ON THE LOWER LIP OF YOUNG BOY



FIG. 13. MUCOUS PATCHES ON THE TONGUE OF YOUNG GIRL



FIG. 14. SECONDARY LESIONS — CONDYLOMATA LATA OF THE VULVA



FIG. 15. SECONDARY LESIONS — CONDYLOMATA LATA OF THE VULVA



FIG 9 CHANCRE OF THE BREAST FROM NURSING INFECTED CHILD

FIG. 10. PRIMARY CHANCRE OF THE PENIS

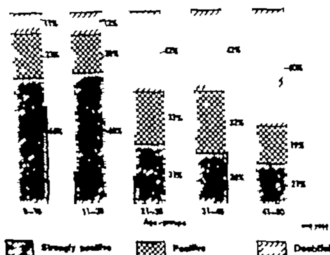


FIG 11 SECONDARY "SPLIT PAPULES" AT THE CORNER OF THE MOUTH OF YOUNG BOY



exhibit the epidemiological and other characteristics of a venereally acquired disease. The use of common utensils, and particularly of drinking vessels passed from mouth to mouth (see fig. 8), offers opportunities for indirect transmission of the infectious agent. Added to this are other unsatisfactory conditions of sanitation found in infected villages, which explain the fairly even distribution of endemic syphilis between the two sexes.

FIG. [illegible]. RESULTS OF SEROLOGICAL EXAMINATIONS (WASSERMANN, KAHN AND MEINICKE) BY AGE-GROUPS IN [illegible] CASES OF UNTREATED LATENT SYPHILIS



Endemic syphilis has all the characteristics of a family disease.[22] Once it has entered a family infection is very often transmitted from one member to another and the simultaneous infection of members of the family is often seen. A study of this type of endemic syphilis was undertaken in 642 infected families. It was observed that the infection-rate among children varied according to the infection of the parents, as illustrated below

	Infection among children (%)
Both parents infected	51.6
Wife infected	38.2
Husband infected	36.3

In 20% of the families examined, the children alone were infected. The occurrence of infection in the children of healthy parents is accounted for by the fact that the children are most exposed to infection when playing together they therefore contract infection outside their homes and bring

FIG. 16. SECONDARY LESIONS — CONDYLOMATA OF THE ANAL MUCOSA



FIG 17 LATE SECONDARY LESIONS — RUPIAL SYPHILIDE OF THE SCALP



FIG 18. EXTENSIVE GUMMATOUS DESTRUCTION OF THE NOSE AND PHARYNX



FIG. 19. OSTEOPERIOSTITIS OF THE TIBIA, WITH HYDRARTHROSIS



CHAPTER 5

NATURAL COURSE OF ENDEMIC SYPHILIS

The natural course of endemic syphilis in Bosnia attracted the attention of syphilologists many years ago. From the impression that certain forms of syphilis appear more frequently than others, or not at all, the *erroneous* conclusion was drawn by Glück [illegible] that the endemic syphilis of Bosnia was a benign disease and of a different kind from sporadic venereal syphilis, with the following special characteristics primary lesions absent secondary symptoms as the first evidence of infection generalized exanthemata rare gummata of the skin and mucous membrane, or of the osteo-articular system, frequent cardiovascular involvement, tabes, or paralysis absent and healthy children born of syphilitic mothers. These observations resulted in a fallacious clinical concept which prevailed for a long time in both national and foreign literature. However as a result of a field survey of large groups of individual clinical cases carried out in 1934 and 1935 by the Zagreb School of Public Health,[illegible] with the financial assistance of the Rockefeller Foundation, it was established that the manifestations of endemic syphilis in Bosnia were actually no different from those of venereally acquired syphilis. Cardiovascular and neurological involvement do occur The apparent absence of certain symptoms or forms of syphilis, including congenital manifestations—or their combination—was primarily due to the epidemiological characteristics of the disease and to environmental factors.

The reasons for which endemic syphilis was previously considered as a benign disease may be explained in part by the psychological reactions of the patients living in primitive conditions.[illegible] [illegible] Since it is a chronic infectious disease which is seldom the direct cause of death and which rarely results in a total incapacity for work, it is not considered by the population, accustomed to living under primitive social and economic conditions, to be so grave a disease as it is by people living under more developed conditions. A destructive gummatous facial lesion or involvement of the central nervous system would have a more serious psychological effect on persons with higher living standards and greater social and economic obligations. When living standards rise and different social and economic obligations are assumed, what appeared to be the "benign" character of the disease disappears. This has become apparent in regions of Bosnia where industrialization and collective living are gradually creating improved conditions among the rural population. Syphilitic manifestations which were previously not taken very seriously are now considered by the people as a

it into their own family The infection of parents by their children and the appearance of primary lesions are sometimes the result.

The spread of infection in a family generally follows certain patterns, although variations obviously exist. First, a husband with syphilis may infect his wife, she infect the younger children, and they in turn, transmit the disease to the older children secondly an infected mother may transmit the disease to the youngest child first, then to the father and finally to the remaining members of the household or thirdly in families where syphilis is introduced by a child, it is usually first transmitted to the mother then to the older children, and lastly to the father However it is often impossible to establish the order in which the infection has been passed on, particularly when early infectious symptoms appear simultaneously in all, or in the majority of the members of the family

While venereal acquisition of sporadic syphilis among married people is facilitated by sexual activity this is not the case with endemic syphilis in Bosnia. Both husband and wife may bring endemic syphilis into the marriage but, as the infection was often contracted in childhood, it is usually in the late or latent stage. Because the marital partners will ordinarily have had the infection for many years, the risk of venereal transmission is considerably diminished.

The following tabulation illustrates the average infection-rates of married couples it should be noted that these are subject to many variations, depending principally on the duration of the infection and on the type and amount of treatment received.

	Percentage of families examined
Wife infected	42.3
Husband infected	29.3
Both partners infected	28.4

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physical and psychological burden and as an obstacle to their further economic and social advancement.

It was partly because endemic syphilis was looked upon as benign that it was felt to be in some way different from sporadic venereal syphilis. In fact, the nature of the clinical and pathological manifestations is similar in both, and treatment with specific drugs has a similar influence [14] the difference is rather in the attitude of the patients and in the natural course of the disease as it is influenced by the environment.

Our present knowledge of that course may be summarized as follows.

Early Infectious Lesions

Primary lesions are seldom observed in endemic syphilis, but they do occur [19] Although their infrequent diagnosis might, in part, be attributable to their localization on parts of the body difficult to observe, this cannot explain the actual rarity of their occurrence in endemic syphilis, since systematic clinical investigations in large population groups with a high infection-rate show primary lesions in less than 1 / of the early cases. An identical situation exists also in other countries where primitive hygiene and living conditions favour a non-venereal transmission of treponemal infections epidemiologically similar to endemic syphilis, such as bejel and " njovera "

The possibility of repeated exposure to infectious material certainly exists in primitive environments, but it seldom leads to the transmission of treponemes in such large numbers as occurs through the more intimate contact of mucous membranes when syphilis is acquired venereally As we have already noted, the common use of domestic utensils, particularly drinking vessels, in Bosnia favours the transmission of treponemes In order to make a rough estimate of the number transmitted, a drinking vessel, or " ibrik " (see fig. 8), was examined by darkfield microscopy shortly after being used by a person suffering from papular lesions of the mouth. Treponemes similar in shape and movement to *T pallidum* were identified in very small numbers. Repeated transmission of small numbers of treponemes probably also takes place in the other usual direct and indirect contacts of everyday life. Occasional transmission of treponemes in large numbers under special circumstances must, however not be overlooked. In fact, whenever primary lesions were found, the infection appeared to have been contracted under circumstances which would favour such transmission, as in primary lesions of the nipple where infection of the mother has taken place quantities of treponemes being transmitted from large oral papulae in the child to the mother s nipple (fig. 9). The repeated and long lasting direct contact in breast feeding obviously facilitates the entry of great numbers of treponemes into the tissue.

The same is the case in endemic areas if one marital partner has infectious syphilis lesions on the reproductive organs: sexual intercourse will then obviously increase the possibility of transmission of a great number of treponemes. Indeed, in endemic syphilis, contagious symptoms are occasionally located on these organs and primary lesions localized on the genitalia have been observed to result, particularly in endemic foci of recent origin (see fig. 10).

The frequency of occurrence of primary lesions depends mainly on the size of the inoculum and on the conditions under which the infection was actually contracted. A typical primary lesion usually develops after massive inoculation with treponemes—as, for instance, in a chancre of the nipple or on the genitalia. On the whole, however, venereal transmission is rare in the Bosnian environment. Conditions there favour the repeated transfer of small numbers of treponemes with resulting lesions in the oral region, and the pathological tissue reaction does not manifest itself at the site of the inoculation in the form of a primary lesion.

This is supported by the findings of Akrawi[1] who, by massive exposure of volunteers to bejel treponemes, obtained primary lesions following scarification of the lip and, under considerably less favourable conditions of exposure, symptomless infection, that is to say seropositivity alone, resulted in a limited number of cases without the occurrence of primary lesions. Animal experiments in syphilis carried out by Morgan[41] and later by Magnuson, Eagle & Fleischman,[36] also confirm that subclinical infection or reinfection can take place under certain experimental conditions.

In endemic syphilis, the early infectious lesions are generally enanthemata and exanthemata of the secondary type. They are usually localized papules, the seriousness of which, especially in the oral region, and if neglected and untreated, is considerable (see fig. 11-13).

Several members of a family often exhibit lesions identical in appearance and location. It has been possible, in the Bosnian programme, to observe the development of the disease in some families from the very beginning of the infection. Persons have been found to be clinically and serologically negative at the first examination in whom subsequent examinations revealed a gradual rise in the serological titre with no noticeable lesions on the skin or mucous membrane, until a typical papular lesion finally appeared in the oral region.

Other Manifestations

Late manifestations of endemic syphilis do not differ from those of sporadic venereal syphilis (see fig. 14-17). In some instances, benign late lesions are rather striking because of the extensive tissue destruction, particularly in neglected cases and when occurring on conspicuous parts of the body[38] (see fig. 18). Such forms, however, are gradually becoming rarer.

Gummatous lesions appear *most frequently* on the skin, in the naso-pharyngeal region, and in the osteo-articular system. Although frequent in children, they also occur in all age-groups.

Affections of the bones and joints call for special attention [3, 34, 37] in some regions they appear in as many as 20% of the cases, the *most frequent* being arthralgia and osteoperiostitis (see fig. 19). More than 80% of the osteo-articular lesions found in Bosnia were symptoms of late syphilis. The great majority of these were the result of syphilis acquired in infancy and not of congenital syphilis.

The question of the involvement of the central nervous system in endemic syphilis long remained a major point of scientific interest, since it was suggested by Glück and his group [10, 14, 15, 17] that such involvement, especially that of the parenchymatous tissues, as in tabes and paralysis, rarely if ever occurred. *Field investigations* carried out in Bosnia in 1934 and 1935 showed, however that all forms of neurosyphilis occur in endemic syphilis, but *that* atypical or stationary *forms* are frequently encountered. [23, 44, 45]

Cardiovascular involvement is also well known in endemic-syphilis areas, *but no accurate investigations have so far been carried out to deter*mine the actual extent of its occurrence.

The rarity of congenital syphilis is discussed in a subsequent section.

Tertiary Lesions as an Epidemiological Index

The occurrence and frequency of tertiary symptoms vary with the treatment provided in different areas. Such variations are described throughout the history of syphilis, from the period of the European pandemic up to the present time. If the features of non-venereal syphilis in various parts of the world today are compared with those appearing at the end of the 15th and the beginning of the 16th centuries, as well as in the 17th and 18th centuries when the disease was endemic in certain countries, *tertiary* symptoms appear to have been very frequent when the disease was actively spreading *tertiary lesions later became* less *frequent*, although they still appear frequently in active endemic areas such as Bosnia. The early accounts of the disease during its active periods there suggest that as much as 50% or more of all clinical manifestations observed were tertiary lesions. A similar situation exists today in rural foci of recent origin, while in areas where endemic syphilis is on the wane the proportion of tertiary lesions is decreasing. In such areas the incidence of tertiary symptoms is no higher than that found in sporadic venereal syphilis.

Various attempts have been made to explain why tertiary symptoms appear to have been frequent during those periods when syphilis was spreading actively in Europe, and why on the other hand, they are relatively rare today in *sporadic venereal syphilis* and to explain why such lesions

remain frequent in active endemic-syphilis areas, such as Bosnia, where primitive living conditions still exist.

The existence of biologically different strains of treponemes—dermatotropic or neurotropic—with selective affinity to certain types of tissue, has not been conclusively demonstrated, nor is it likely that ethnological peculiarities [38] in the host account for variations in the occurrence of different forms of syphilis. It is certain, however, that therapy plays an important role, since adequate treatment of syphilis will prevent the appearance of tertiary and other late symptoms. In inadequately treated cases, treponemes remain in the human host and may sooner or later become activated under the influence of various exogenic or endogenic factors. This will give rise to pathological changes in an already allergic organism, resulting in tertiary and other late syphilitic manifestations. The influence of treatment, however, gives only a partial explanation, since there exist geographical areas in the world today with a high percentage of inadequately treated, or even untreated, endemic syphilis where tertiary lesions are comparatively rare and no more frequent than in areas with sporadic venereal syphilis.

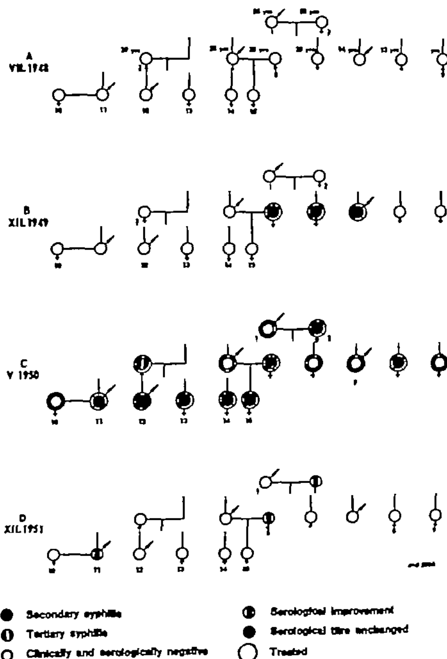
It is important to bear in mind that, wherever tertiary manifestations are frequent in endemic areas, the reservoir of *T. pallidum* is always extensive, as is shown by the numerous fresh cases of early infectious syphilis that occur, and that the primitive living conditions afford repeated opportunities for the perpetuation of the disease by direct and indirect contact. Many years ago Glück [23] observed, in families where fresh infections occur, that gummatous lesions may appear in some members of the household either simultaneously with, or some weeks after, the appearance of symptoms of early infectious syphilis in others.

Superinfection of an already infected and allergic host by treponemes is considered to be the chief reason for the large number of tertiary manifestations in active endemic-syphilis areas.

In fresh rural foci of endemic syphilis where the initial infection takes place in early childhood, the subsequent natural course of syphilis will result in immunobiological changes with an altered reactivity of the organism to further invasions of treponemes. Little obstacle is opposed to repeated invasion of a sensitized human host [61] by treponemes from the infected surroundings so long as the primitive living conditions of the population remain materially unchanged.

In this connexion a systematic examination carried out on an entire family is of particular interest (fig. 21). The family consisted of fifteen persons, all of whom proved clinically and serologically negative at the first examination, including the eldest son (No. 3), who had received salvarsan treatment for syphilis 18 years before. The first control examination carried out 17 months later showed that a fresh infection had developed in the family. Early infectious lesions first appeared in three members

FIG. 21 SIMULTANEOUS APPEARANCE OF SECONDARY AND TERTIARY SYPHILIS IN A FAMILY WITH AN ACTIVE FOCUS ([illegible] DAKULE)

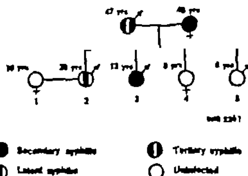


(Nos. 5 6, and 7) and some months later seven more were infected. At the same time the eldest son reacting differently from the rest of the family as a result of his previous *infection, developed tertiary syphilis,* showing

gummatous lesions of the pharynx with tissue destruction, and became serologically positive (Kahn and Meinicke (MKR II)).

In another family (fig. 22), the father 47 years old, had been treated for syphilis with salvarsan and bismuth 10 years previously. His wife had a negative anamnesis of syphilis. A systematic examination showed that the mother and a 13-year-old child both had early infectious syphilis lesions in the form of hypertrophic papules on the tongue and tonsils the father on the other hand, had nodulo-ulcerous gummata on the skin in the gluteal region. The eldest child, 20 years of age, was in the latent stage.

FIG. 22. SECONDARY AND TERTIARY SYPHILIS IN A FAMILY WITH A FRESH FOCUS (NINO SIROSNICA)



The situation in this family must be interpreted as meaning that, while the mother and one child had early infectious syphilis as a result of a first inoculation with treponemes, the father who had been infected and inadequately treated 10 years before, exhibited tertiary symptoms because of re-exposure and superinfection. The difference in the immunobiological reactivity or response in these persons was reflected in the resulting clinical manifestations.

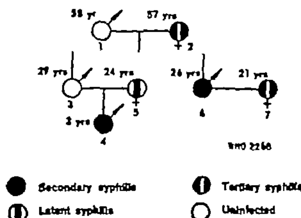
In a third family (fig. 23) two of the members (Nos. 4 and 6) exhibited symptoms of early infectious syphilis simultaneously while two others (Nos. 2 and 7) had gummatous destruction of the tissue of the soft and hard palates. The latter two were the grandmother, 57 years of age, whose history showed that she had been treated for syphilis 50 years before, and a young woman, 21 years old, treated for oral symptoms of frenga at the age of 11

A further example is the case of a young wife who developed gummata while her husband developed early infectious secondary syphilis. The

possibility of the wife's escaping new exposure to treponemes under such circumstances is remote.

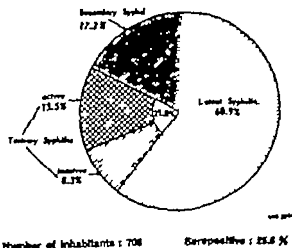
Should living conditions improve and the chances for non-venereal transmission of treponemes decrease, or should treatment be given, the

FIG. 23. TERTIARY SYPHILIS IN A FAMILY WITH A FRESH FOCUS (WHO SAPNA)



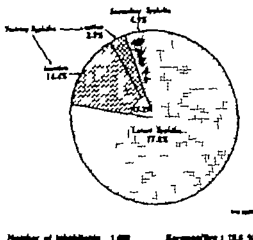
number of new cases with active tertiary lesions will diminish in endemic areas. The relationship of early clinical syphilis to active tertiary manifestations has already been illustrated in several ways. We may illustrate it further from the observations made in two villages where the incidence of various forms of syphilis was recorded. In Kosova (fig. 24) a high

FIG. 24. DISTRIBUTION OF SECONDARY AND TERTIARY SYPHILIS (KOSOVA)



prevalence of disease was found (25.6%) and the reservoir of infection was extensive. Of the cases found, 17.3% were early infectious (secondary), 60.9% were latent seropositive, while tertiary syphilis accounted for 21.8%. Of that 21.8%, 13.5% had tertiary symptoms of recent date and 8.3% showed scars of tertiary lesions which had occurred some time before. This represents, therefore, a focus of endemic syphilis which had persisted for a considerable time but which was still spreading actively. Numerous further cases of tertiary syphilis must be expected in this area.

FIG. 25. DISTRIBUTION OF SECONDARY AND TERTIARY SYPHILIS (BILJE)



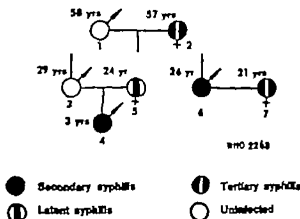
A different situation prevailed in Bilje (fig. 25). Here the general infection-rate was also comparatively high but with a relatively small number of early infectious (secondary) syphilis cases (4.9%). A very small percentage (2.9) of new cases with recent tertiary lesions was found, while a much higher percentage (14.4) showed signs of old tertiary lesions. The latter had developed when the endemic focus had been spreading actively. As the reservoir of treponemes gradually lessened, the possibility of reinfections and superinfections diminished, and the number of cases with fresh tertiary manifestations consequently decreased.

The pathogenesis of tertiary syphilis in such cases can best be interpreted on the basis of repeated treponemal invasions in already sensitized allergic organisms. Considerable support for this is found in the numerous laboratory and other investigations carried out by Finger & Landsteiner,[13] Chesney,[7] Brown & Pearce, Magnuson,[42] and others. These investigators have shown that superinfection can take place in an already infected host. As a rule, such reinfection results in a pathological reaction in the sensitized host[42] with a development of the late destructive type of syphilitic lesions.

possibility of the wife's escaping new exposure to treponemes under such circumstances is remote.

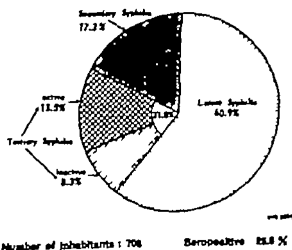
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ally decreases with time. In addition, the likelihood of an infected woman s transmitting the disease to her offspring will, as is well known, decrease with time and with the number of pregnancies. Since venereal syphilis is usually contracted after the person has attained maturity the likelihood of congenital syphilis in the children is considerable for some time. In endemic syphilis, however many years generally elapse, in both males and females, between the acquisition of infection and the attainment of maturity the probability of the mother's giving birth to congenitally syphilitic children is thus reduced from the outset. Secondly the low standards of hygiene of the population of endemic-syphilis areas generally result in a high neonatal-mortality-rate. In the rare cases of congenital syphilis in such areas, the life expectancy is consequently further reduced, particularly if little or no treatment is available.

Although no exact data can be given as to the actual incidence of congenital syphilis in Bosnia, it must be expected to be relatively infrequent.[11, 49] An investigation was carried out during the present campaign to determine whether the mother infected with endemic syphilis, would transmit treponemes through the placenta to the offspring. This was done by comparing infected and non-infected groups of women both of whom lived under the same conditions in an area with an average infection-rate of 27%.

The results are tabulated below

	Infected mothers	*Healthy mothers*	*Total*
Number of mothers	141	134	775
Pregnancies	832	766	1,618
Normal infants	797	718	1,515
Miscarriages	55	48	103
% of pregnancies	*6.4*	*6.3*	*6.3*
in first half of term	21 (38.2%)	30 (62.5%)	51 (49.5%)
in second half of term	34 (61.8%)	18 (37.5%)	52 (50.5%)

In 42 miscarriages observed, the situation was as follows

	Infected mothers	*Healthy mothers*
Premature infants	10	8
Stillborn infants	17	7
Total	27	15

It is suggestive that there is a higher rate of stillbirths in women infected with endemic syphilis this is the result of diaplacental infection. Although some congenital syphilis occurs, it is relatively rare in the living child population.

The high general neonatal-mortality-rate found in infants in this particular region is a reflection of the low standards of hygiene. This is

When, therefore, a host which is already in a stage of late or latent syphilis is reinfected, no primary or secondary lesions will result however lesions of the tertiary type, accompanied by rapid tissue destruction, may appear It is likely that a similar situation also exists in other treponemal diseases, such as bejel and yaws.

Laboratory experiments have shown that reinfection may result without lesions developing at the actual site of inoculation [8, 44] and that asymptomatic infection may occur [8, 8] Magnuson & Rosenau [49] have tried to analyse this type of relative immunity by determining quantitatively the number of treponemes which will bring about reinfection under controlled conditions. They conclude that, when asymptomatic reinfection occurs, this indicates that a partial immunity exists sufficient to destroy the majority of the treponemes and to prevent a lesion from developing at the site of the inoculation, but not sufficient to destroy all the treponemes, which will continue to penetrate into the host. These experiments have shown that this modified reactivity in the host may persist even if treponemes do not survive in the body after infection.[7, 49]

Thus tertiary lesions may develop for one of two reasons. First, there may be reactivation of residual treponemes in a sensitized allergic organism, upsetting the parasite-host relationship This occurs in untreated or inadequately treated sporadic venereal syphilis it may also occur in endemic areas, usually in the stationary or regressive period, but it is probably of secondary importance. Secondly tertiary lesions may develop from superinfection of the host which is already in an allergic state as a result of prior infection. In such cases, any residual dormant treponemes in the host are likely to be of little importance the essential features are the host s changed reactivity and allergic state.

From the observations made and the results of the campaign in Bosnia, we may conclude that it is largely due to the environmental factors which influence the natural course of the disease in endemic areas, and which are the chief cause of reinfection and superinfection, that the late manifestations of syphilis appear early particularly tertiary lesions in already sensitized hosts, and that the frequency with which such lesions occur represents an epidemiological indication or index of the state of activity of the rural endemic foci, and of whether their origin is more or less recent.

Rarity of Congenital Syphilis

It was previously thought that the non-occurrence of congenital syphilis was one of the characteristics of endemic syphilis. The following facts, which are consequent upon the epidemiological and environmental considerations we have already advanced, help to elucidate this problem. First, in untreated, and even more so in treated, syphilis, the infectiousness gradu-

CHAPTER 6

ORGANIZATION OF THE FIELD CAMPAIGN AGAINST ENDEMIC SYPHILIS

In organizing any mass campaign against endemic syphilis, or against any other treponemal disease with similar epidemiological features, such as bejel or yaws, methods of procedure should first be laid down which take into account the characteristics of the environment and the particular epidemiological features of the disease arising from it.[31] The present programme in Bosnia was begun in 1948, and the following criteria were adopted for the field campaign as it proceeded from district to district, and will continue to be used until the end of the programme

1. Case-finding should be carried out by systematic serological screening of the entire population in addition to clinical inspection.

2. Adequate free treatment should be provided for all diagnosed cases of endemic syphilis and should be obligatory

3. Follow-up re-examination of infected areas should not be confined to the cases diagnosed and treated during the initial survey but should also include re-examination of the remainder of the population at intervals, until a satisfactory epidemiological situation has been established and consolidation of the results has been achieved through the regular public health services.

4. Data should be recorded and control and follow-up measures established on a family basis, and the individual cards of infected persons should be an integral part of the family record since the family is the basic social as well as epidemiological unit in Bosnia affected by endemic syphilis.

5. The active collaboration of the population in carrying out the programme should be secured, interest in health work should be stimulated, and health consciousness should be developed as part of a more general effort to improve living conditions in rural areas.

6. The methods and the public-health principles applied should be similar throughout the areas in which the programme is being carried out.

Three field groups, or teams, were originally organized, each being composed of from eight to ten members of the national medical and auxiliary staff. The team leaders were capable medical workers with fairly extensive experience in specialized institutions and in the field. The teams did not always have a medical officer attached, but the co-operation of the health officer of the district in which the team was stationed was secured in order

illustrated by the following figures, showing the mortality among 200 infants born of infected and healthy mothers

	Born of infected mothers (%)	Born of healthy mothers (%)
Infants surviving more than one year	68.2	73.9
Infants dying before one year	31.8	26.1

Thus the mortality-rate among children under one year of age born of infected mothers is 5 7 / higher than among children of healthy mothers. It will also be seen that loss of infant lives due to syphilis is relatively small, and consequently the proportionate mortality from congenital syphilis may hardly be noticed despite the high endemic-syphilis infection-rate.

It is a striking feature of the environmental conditions that the high infant mortality rate is somewhat compensated for by a high birth-rate. During the present study it was found that infected mothers had an average of 9 1 pregnancies up to the age of 45 whereas healthy mothers had an average of 8.8. This difference was balanced by the difference in mortality- and survival-rates of children in both groups just mentioned.

It might have been expected that regions with the highest prevalence of endemic syphilis would also show the lowest birth-rate, the highest infant mortality-rate and the smallest increase in population but, although it may appear paradoxical, the highest birth-rate and the most marked population increase were often found in the most highly infected areas. The explanation for this may be on the one hand, that in the most highly infected areas conditions are very primitive and little or no restraint is associated with sexual life, with the result that conceptions are frequent and, on the other hand, that, since the infection is generally acquired in childhood, the risk of diaplacental transmission of treponemes is considerably reduced.

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Three field groups, or teams, were originally organized, each being composed of from eight to ten members of the national medical and auxiliary staff. The team leaders were capable medical workers with fairly extensive experience in specialized institutions and in the field. The teams did not always have a medical officer attached, but the co-operation of the health officer of the district in which the team was stationed was secured in order

to provide adequate medical supervision. The investigation and study of epidemiological and clinical problems, in particular the use of penicillin in endemic syphilis, and the central technical supervision of the team were the responsibility of the syphilologist in charge of the central dispensary from which the campaign was directed. Each team had a serological field-laboratory at its disposal, manned by responsible technicians practised in carrying out serodiagnostic tests for syphilis. Qualitative Kahn and Meinicke (MKR II) tests were carried out on all blood samples. It was not possible to perform quantitative as well as qualitative tests in all parts of the field quantitative tests were therefore confined to special pilot, research, or control areas. The average testing capacity of a field laboratory amounted to approximately 600 serological tests a day

Each team was made responsible for a district at a time. There was an average population of 30 000 to 40 000 inhabitants in each of the 19 districts so examined up to the end of 1951 The districts are divided into smaller administrative units (MNO), each having approximately 8 to 10 villages and 2,500 to 3,500 inhabitants.

Each team had field cars at its disposal which would take the team members from their headquarters to auxiliary sub-units or as was more frequently the case, team members would have to walk for several hours through mountainous country to the hamlet in which a working base was established.

Teams would generally be divided two team members working in each village. Field facilities would be improvised at a community centre or in a suitable house or hut. The inhabitants had always been informed in advance either by the national authorities, through existing local organizations, or in preliminary conferences, of the purpose of the work. This type of health education proved very valuable.

The blood samples collected during the day were carried by special courier to gathering points by the road where a car would take them to the laboratory for examination. Blood samples always reached the laboratory on the day they were drawn and, even during hot summer months, haemolysis was very rarely observed.

All cases of syphilis detected clinically were treated immediately On the basis of serological examinations carried out on the entire population in the area, treatment was also given to those persons with positive serological reactions. Six to eight days were usually required to examine systematically the population of each administrative unit (MNO), while the time devoted to treatment varied according the schedule used.

A family record was made of all infected families found in the villages this included the individual card of each infected member of the family together with a record of all clinical and serological examinations, treatment, control examinations, and any other relevant material The record system used for the systematic serological examination of the entire population in

the villages and surrounding rural areas was based on the latest census data (1948). A very valuable record of the infected families was thus constituted without this information no statistical analysis of the data would be possible.

In the villages there were generally no houses more than half an hour's walk from the place of examination. Although treatment was obligatory for persons found to be infected, the degree of voluntary co-operation was high and, with very few exceptions, no compulsion proved necessary

The team members remained in the villages or at field stations until systematic examination had been completed and treatment given. This had a favourable psychological effect on the inhabitants. In addition, since there were no set working hours for the team or "clinic hours" for the peasants, they could be examined and receive injections all through the day thus rendering any interruption of their agricultural or other work unnecessary This arrangement resulted in a good response to the programme as the people saw for themselves the numerous cases which were effectively helped, increasing support was given to the campaign. Follow-up examinations could consequently be carried out with less difficulty and more rapidly than had sometimes proved to be the case in the initial survey and examinations.

A diagnosis of syphilis was established on the basis of anamnestic data and clinical and serological findings. The epidemiological situation was taken into account in cases of doubtful serological reactions with no clinical signs or history of syphilis. If such reactions remained unchanged or became stronger on the first follow-up examination, this was considered symptomatic of syphilis in families where one or more of the other members had a confirmed diagnosis of the disease.

During the initial period of the campaign, the percentage of the population examined was relatively small. Later as the teams gained experience, some 85 % of the total census population was serologically examined during the first visit of the team during the subsequent control examinations this proportion was increased to approximately 95%. Thus, in families where active infections were found, only on rare occasions would a member of the family fail to be examined at one time or another

The small proportion of the population which escaped the case-finding consisted mostly of persons who had been absent from their homes for some time or of very young children in healthy families. Under the difficult conditions of the field work, it was sometimes not easy to obtain blood samples from young children. The prescribed penicillin treatment was completed in almost 100 % of the cases. This fact should be compared with the unsatisfactory results of previous efforts with salvarsan and bismuth when only some 15 % or 20 % completed their treatment.

At the start of the campaign, the tempo, expressed in the amount of ground covered, was much more rapid than later on, since the same teams had to return to regions previously examined in order to carry out control

examinations As the number of areas examined increased, the rate of extension to new regions decreased.

From the beginning of the campaign at the end of 1948 up to the end of 1951 systematic examinations and treatment of endemic syphilis were carried out in 19 districts, the teams completing work in one district before moving to another Some 438,863 serological screening examinations and 113 158 serological control examinations, or a total of 552,021 blood tests, were carried out by the field laboratories. During this period, 35,238 cases of syphilis were diagnosed and received treatment, corresponding to 8.1% of the population examined.

The following tabulation illustrates the distribution of the different stages of syphilis found

Form of syphilis	*Cases*	*Percentage of total*
Early infectious lesions and primary	3 422	9 71
Congenital	7	0.22
Latent	29 881	84.8
Late	1,928	5 47
Total	35,238	100

There was considerable variation in the prevalence of disease from district to district, it ranging from less than 1% to 13% or more. In some smaller administrative units and villages, it was often found to be considerably higher The average infection rate of 8 1% therefore does not give a true picture of the distribution. The relevant data on this point will be found in the section dealing with the epidemiology of endemic syphilis. As the highest infection-rate was found in north-eastern Bosnia (see fig. 4) the most intensive field work was done in that region. In assessing the importance of the disease in the different areas, consideration was given not only to its general prevalence but particularly to the proportion of early infectious cases, since that is an indication of the degree of activity of the endemic focus. Thus, in the district of Lopare, with an average infection-rate of 12.5% only 6.7% of the total number of infectious cases were in the early infectious stage while in the district of Tuzla, where only 6.3% of the population was infected, the percentage of early infectious cases was 11 4 The most extensive reservoir of infection was found in the district of Gračanica, where as many as 42.4% of the total number of infected cases had early infectious lesions. In Tešanj and Gradačac the figures were 13.8% and 8.8%, respectively The lowest rates were found in the districts of Visoko and Zenica, with 1.5% and 1.9% of infectious lesions, respectively

The proportion of fresh cases of syphilis constitutes an important epidemiological indication as it expresses the extent of the pool of immediate

infectiousness in a particular area. Priority was therefore given in the present campaign to action in areas with the highest proportion of early lesions, where the initial task was to control the further spread of infection from such active foci in the shortest possible time and, if possible, to eliminate them completely. It is obvious that this is more important in a public-health programme than to begin work in areas where the endemic is stationary or receding. The task of reducing the reservoir of potential late manifestations of syphilis by treating late latent cases is of secondary importance in the initial phase of the campaign when areas are selected for action.

CHAPTER 7

TREATMENT OF ENDEMIC SYPHILIS WITH PAM AND SCHEDULES EMPLOYED

In the campaign against endemic syphilis, the use of procaine penicillin G in oil with 2 / aluminium monostearate (PAM) proved decisive in solving this health problem. PAM was used regardless of the stage of the disease and its value in the treatment of syphilis, in view of its non-toxicity its rapid effect, the short period of treatment and the facility of administration, was confirmed during the present field campaign.

Combined penicillin and arsenic treatment was not used. During the initial stages of the campaign, however some groups of patients were treated with PAM combined with bismuth. Subsequent control studies of these groups indicated that the results were not different from those obtained with PAM alone. The combined treatment regimen was therefore soon abandoned, and PAM alone was subsequently used.

The treatment schedule used for adults was 3 600 000 to 4,200 000 units, given in six or seven injections of 600,000 units of PAM administered daily or every second day More recently investigations have been carried out in limited areas in the use of a smaller number of injections In two administrative areas the treatment was a single injection of PAM, one group receiving 1 500 000 units and another 3 600 000 units this will be dealt with in greater detail when clinical and serological results are considered.

The criteria for re-treatment were as follows

(1) clinical grounds clinical relapse or reinfection

(2) serological grounds

(*a*) persistent positive reaction to serological test for syphilis (STS) at re-examination 8 to 12 months after initial treatment

(*b*) increased STS titre on re-examination

(*c*) negative STS titre becoming positive.

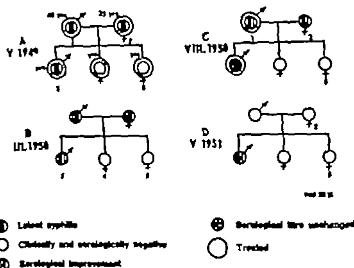
The re-treatment schedule used was usually identical with the original treatment schedule, except when a subsequent control examination showed seroresistance. The amount of PAM was then increased by either half or an entire dose up to a total of 7,200 000 units and applied in a shorter period of time (five days) *There was some variation in the treatment* depending on the individual case.

The PAM used met the minimum requirements proposed by the World Health Organization.

Penicillin was well tolerated, and even elevated doses were sometimes given in a single injection. Marked Herxheimer reactions were occasionally observed, particularly in fresh cases of syphilis. In some few cases urticaria developed. There was, however, no instance where treatment was interrupted because of non-tolerance or because reactions were too marked.

The value of penicillin as demonstrated in the Bosnian campaign should be considered from the point of view both of the clinical and serological results and of the epidemiological results.

FIG. [illegible]. RESULTS OF PAM THERAPY WITH [illegible] UNITS

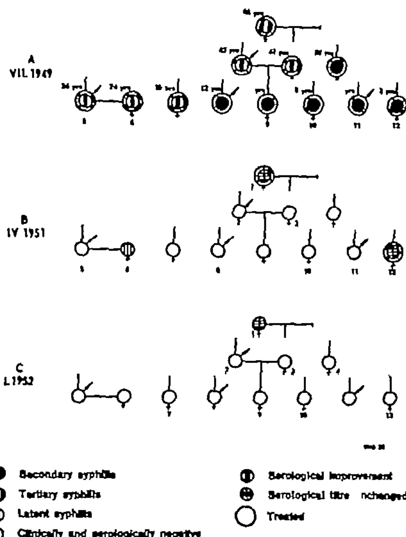


Clinical and Serological Results

The early clinical symptoms in endemic syphilis disappeared as rapidly after treatment with PAM as they do in sporadic venereal syphilis. No case of endemic syphilis in the early clinical stage was encountered which did not respond favourably to treatment. The development of gummatous lesions was rapidly arrested and, if tissue destruction was not too advanced before treatment was begun, restoration of the affected function generally followed. An exceptional case was that of a young female who had many gummata on the skin and in the osteo-articular system and who did not respond even to elevated dosages and repeated injections of PAM.

On the whole, osteo-articular lesions responded well to PAM treatment, although certain lesions (hydrarthrus and various destructive lesions of the osteo-articular tissues) also required orthopaedic rehabilitation methods.

FIG. 27 RESULTS OF PAM THERAPY WITH 4,200,000 UNITS (WHO SREBRENIK)



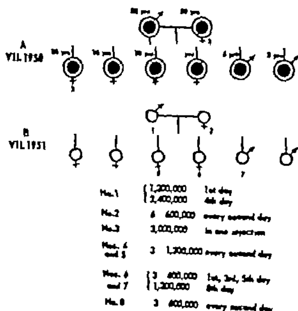
Arthralgic pains responded well to PAM in early as well as in late syphilis. *Cephalalgia and some symptoms no doubt arising from involvement of* the nervous system improved rapidly and often disappeared completely The serological response to PAM as to other antisyphilis drugs, depends *primarily on the duration of the infection.*

In evaluating both the serological and the clinical results, the same principle has been taken as a basis, that is, the results have been evaluated primarily *in terms of the family unit,* the household, and the community rather than of the infected person individually This approach provides an opportunity *to* study the problems of relapse, reinfection, and seroresistance, *the value of abortive treatment,* and so on—matters which the existing literature has so far not sufficiently dealt with in terms of the family

We may cite the following examples to show how the effect of PAM treatment is clearly reflected in the total findings on members of families. The most rapidly declining serological titres were found in families with syphilitic infections of recent date. In one family of five, all, from the grandfather to the grandsons, were syphilitic, with secondary symptoms and positive serological reactions. The entire family was treated simultaneously with PAM in single doses of 600,000 units every second day up to a total of 3,600,000 units each, the children, however being given smaller doses. A series of control examinations showed that three members of the family were serologically negative after 6 months, four after 20 months, and the whole family after 27 months.

In another family of six members, the mother and eldest daughter were in the latent stage, with strongly positive serological reactions, and the other four members, in the secondary stage. The treatment schedule employed consisted of seven injections of 600,000 units of PAM for adults the eldest

FIG. [illegible]. RESULTS OF PAM THERAPY WITH DIFFERENT SCHEDULES ([illegible])



daughter aged 22, and the boy aged 18 were given in addition, 10 ml of bismuth subsalicylate (10 / emulsion) At the first follow-up examination, ten months after treatment, the family was clinically and serologically negative with the exception of the eldest daughter and her 6-year-old sister both of whom showed serological improvement. Further examination 15 and 24 months after the original treatment showed the whole family to be negative. In this particular family latent syphilis responded as well to treatment as did the early secondary cases. The infection was probably introduced into the family a short time before treatment started, and it is therefore likely that these were early latent cases.

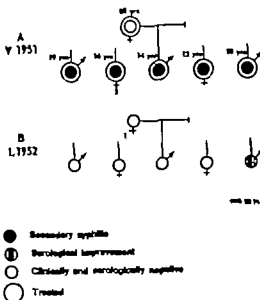
In a third family (fig 26) there were three cases of latent syphilis. The serological titre had decreased gradually 10 and 16 months after treatment. In No 1 it fell from 16 Kahn units to 8, and finally to 4 in No 2, from 256 units to 8 after which the findings became negative in No 3 from 128 to 8 The father and the eldest child (No 3) were re-treated with the same dosage and, when the control examination was carried out after a further eight months, or 24 months after treatment had been begun weakly positive reactions were found in the eldest child, while the others had all become negative.

In a further family (fig. 27) all twelve members were infected with syphilis, but of different stages. After treatment with 4,200,000 units of PAM the entire family became clinically and serologically negative, including those in the secondary and latent stages (probably early latent), with the exception of the eldest member of the family (No 1), aged 66 who had tertiary syphilis. The gummata healed completely after treatment, but the serological findings remained positive even after repeated treat ment, as is often the case in late forms of syphilis of long duration.

The use of different treatment-schedules but approximately the same amount of penicillin (3 600,000 to 4,200 000 units given over different periods of time up to 13 days) showed no significant difference in the results. An interesting example is given in fig. 28. A fresh case of endemic syphilis was introduced into the family and the infection was subsequently transmitted to the whole household. Different schedules of treatment were used, the usual total dose being 3 600 000 units. When the control examination was carried out one year later all members were found to be clinically and serologically negative, irrespective of the schedule of treatment employed.

It was noted during the campaign that, with a total dosage of 3 600 000 to 4,200,000 units, no differences occurred whether the dose was given in single injections, in three injections of 1,200,000 units each on the first, second, and fifth days, or in six or seven injections of 600,000 units daily or every second day In choosing the treatment schedule to be adopted, account was taken of the topographical difficulties in the areas examined and of the number of cases found. The schedule used at the beginning

FIG. 23. RESULTS OF PAM THERAPY WITH SINGLE INJECTION OF 2,400,000 UNITS ([illegible])

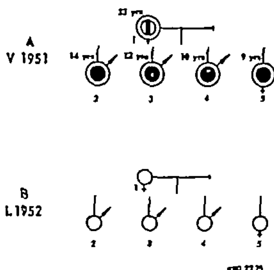


of the campaign usually consisted of a large number of injections, and the team members would stay in the field for some time, remaining in direct contact with the population. Later during the control examinations, the number of injections, and therefore the duration of treatment, was reduced, although the total dosage of PAM remained unchanged.

In cases of seroresistance, a larger dose of PAM was given over a shorter period of time, usually three injections of 2,400,000 units on the first, third, and fifth days. In many instances considerable serological improvement or negative serological reactions resulted six to eight months later. The application of such a dosage certainly adds to the duration of the effective concentration of penicillin in the blood considered necessary [43] in the treatment of early syphilis (0.03 units per ml). However it is not yet known what concentration of penicillin is necessary in the body tissue,[44] or for how long, in order to achieve a complete therapeutic effect on residual treponemes. The experience gained in the Bosnian programme supports the view that larger doses of repository penicillin should be given over a short period rather than smaller doses over a longer period. It was occasionally impossible to administer the routine schedule, and the total dosage of PAM was then given in a single injection. At the follow-up examinations, the results in those cases were found to

be in no way inferior to those obtained with other treatment-schedules. This preliminary observation tends to confirm the view of Thomas and his collaborators [12, 59, 60] and of many others [4, 43, 47] as to the high proportion of cures in early syphilis that can be achieved with a single injection of PAM.

FIG. 30. RESULTS OF PAM THERAPY WITH SINGLE INJECTION OF 3,[illegible] UNITS (MHO SUCESKA)



Secondary syphilis
Latent syphilis
Clinically and serologically negative
Treated

In order to examine the matter further an investigation was carried out on two groups of cases. One group consisted of 110 cases of syphilis, of which 31 were in the early infectious stage, 70 in the latent stage, and 9 in the tertiary stage. The treatment given was 12 ml of PAM totalling 3 600,000 units, 6 ml in the glutaei on each side. At the same time abortive treatment was given to members of families who were likely to become exposed to the infection but who had no symptoms of syphilis at the time of the examination. This was done in order to avoid the risk of reinfection which would have prevented accurate evaluation of the results. The first control examinations were carried out eight months after treatment. Fig. 29 and 30 show two families in this group, before and after treatment. The results speak for themselves.

The second group of cases showed only a few new infections. Of 156 cases, 9 were secondary 136 latent, and 11 tertiary This group was given a smaller dosage of PAM than the first, receiving 1,500,000 units in a single injection. In addition, children who might be exposed to infection were given abortive treatment. The number of patients treated is small, but the following tabulation gives an indication of the serological results 24 months after treatment

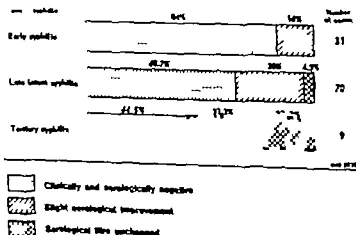
	Secondary syphilis	Latent syphilis
Seronegative	7	121
Improved	2	10
No change	—	5
Total	9	136

The Bosnian programme has afforded only limited experience in the use of single injections of PAM yet, although it is too soon to draw any definite conclusions, the results observed so far are not inferior to those obtained after two years with a larger number of injections, even when the total dosage is reduced to 1,500,000 units of PAM.

The following information may give a clearer picture of the total results obtained in the treatment of endemic syphilis with PAM.

In the administrative unit of Srebrenica in the district of Gradačac, where there was a prevalence of 21.8 ‰ control examinations were carried out over a period of 36 months on 443 cases out of a total number of 503 originally examined, or 87.2 ‰ each of which had received 4,200,000

FIG. 21 RESULTS 8 MONTHS AFTER PAM THERAPY WITH SINGLE INJECTION OF 2,400,000 UNITS (BIHO SUCESKA)

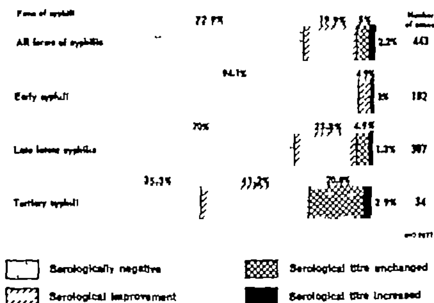


units of PAM in seven injections 102 of these were cases of early syphilis, 307 were in the late latent stage, and 34 had tertiary syphilis.

Fig. 31 gives the total clinical and serological results of this first group, which are considered highly satisfactory The clinical manifestations responded as well to this schedule of treatment as they did to the more protracted schedules.

Fig. 32 gives details of the serological findings in Srebrenica 36 months after treatment. The best results were achieved in secondary syphilis, where 94 1% became seronegative. During the two follow up examinations, 14 5% of the patients were re-treated with the same dose of PAM.

FIG. 32. RESULTS 36 MONTHS AFTER PAM THERAPY WITH 4,200,000 UNITS IN 7 INJECTIONS (MINO SREBRENIK)



Teočak, in the district of Lopare, was an old receding endemic focus with 4 198 inhabitants 721 cases of syphilis were diagnosed, 17 of which showed symptoms of early syphilis. The treatment schedule used was 3,600,000 to 4,200 000 units of PAM When the control examination was carried out three years later 76 6% of all treated cases had become seronegative. Re-treatment was carried out in 26 1% of the cases.

It is difficult to establish the best moment for re-treatment, except in cases of clinical and serological relapse, or in seroresistant cases of early syphilis.[68] When serological findings remain positive or decrease insignificantly after an adequate dosage of penicillin, it is not yet known for how long re-treatment can be delayed in individual cases without harm to the patient.

In mass campaigns the question is even more complicated since there may be no permanent facilities for periodic examination at short intervals of the cases found during the initial survey. Control examinations are usually carried out at fairly long intervals, and a decision as to whether re-treatment is necessary has to be made immediately. In the Bosnian campaign, it was usually decided to give re-treatment to cases, especially those of early syphilis, which under other circumstances would merely have been kept under observation. In the more closely supervised control areas, however, the situation was different. Thus, in one administrative unit, in the district of Zvornik, where there were 328 cases of syphilis, 12 had fresh secondary lesions, and no re-treatment was given for 24 months. All cases were originally given a total dosage of 3,600,000 units of PAM in six injections. Family contacts, representing 18% of the infected cases, were also treated with the same dose. This proportion corresponds approximately to the number of cases usually re-treated. A control examination made two years after treatment showed the following serological results:

	Secondary syphilis (%)	Latent syphilis (%)
Seronegative	86.5	79
Improved	13.5	16.3
No change	—	3.7
Serological relapse	—	1.0
Total	100	100

The results do not differ materially from those obtained in series of patients where re-treatment had been given. It would seem, therefore, that re-treatment may be delayed in certain groups. Control examinations, however, should take place at intervals considerably shorter than two years so that fresh cases will not become foci for the further spread of infection in the area, and those cases should be detected and treated as early as possible.

The immediate epidemiological results which may be expected after the initial examination and treatment of endemic syphilis in a mass campaign depend on several factors, the most important of which are:

(1) the precision and completeness with which the systematic examination of the population and the treatment of infected cases and family contacts are carried out,

(2) the extent of the reservoir of infectiousness at the beginning of the campaign and of the residual reservoir after initial treatment, and

(3) the extent of population movements within one area and among neighbouring areas.

When these factors are favourable and tend to restrict the disease, a long interval between the initial and the follow-up examinations may still allow of good results. But in circumstances favouring the spread of the disease, and where there is an extensive reservoir of infection, satisfactory results cannot be expected.

Epidemiological Results and the Necessity of Abortive Treatment of Contacts

Although the Bosnian campaign is not yet completed and data are not yet available for the entire area, it is nevertheless possible to give some indication of the type of epidemiological results which can be achieved.

In addition to the example already given, we may mention the systematic campaign carried out in the district of Lopare from the end of February to May 1949 during which 3,269 cases of syphilis were discovered and treated, a prevalence of 12.5 %. Of the infected cases, 221 showed symptoms of early infectious syphilis. When the first follow up examination was carried out 14 months later 35 cases of early infectious syphilis were found, of which 32 were new and 3 were relapses or reinfections. Thus, contagious manifestations of syphilis had been reduced by 84.2 %. The treatment was 4,200,000 units of PAM Family contacts were not treated at the time.

So far as the 32 new cases of syphilis were concerned, 37.5 % came from families in which there were already infections, while the other 62.5 % were members of families where no cases of syphilis had been detected 14 months previously It is obvious, therefore, that when follow-up examinations are carried out, especially in areas where there are actively expanding foci, every effort must be made to discover the new sources of infection, not just among those previously treated but among the entire population of the area. When the campaign started, it was believed that the chief risk in perpetuating the disease came from infectious relapses in cases where treatment had failed. It became evident, however that the important potential sources of infection were represented by infected persons who remained untreated through being absent or otherwise escaping examination by new cases of syphilis imported from other areas as a result of population movements, and particularly by symptomless cases in the incubation period at the time of the original examination in which infectious lesions subsequently developed.

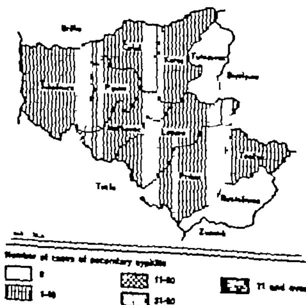
The geographical distribution of secondary syphilis in the administrative units of the district of Lopare, before and after the systematic field campaign, is given in fig. 33 A second control examination of the entire population is being carried out at the time of writing, three years after the start of the campaign and 22 months after the first control examination, at which time abortive treatment was given to all contacts in families where fresh cases of syphilis had occurred and 23.7 % of the cases received

FIG. [illegible]. DISTRIBUTION OF SECONDARY SYPHILIS BY ADMINISTRATIVE UNITS IN DISTRICT OF LOPARE

First Systematic Examination, [illegible] ([illegible] Cases)



Systematic Control Examination After [illegible] Months ([illegible] Cases)



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occurs. It would therefore be impossible to control successfully or rapidly by direct diagnostic means the spread of an infection once it had appeared in a family. It is consequently necessary that all contacts in the family or household be treated with penicillin in order to assure satisfactory epidemiological as well as clinical results.

The amount of PAM used for abortive treatment has varied. At the beginning of the campaign the same amount was used as in diagnosed cases. The abortive dose was gradually reduced to 1,200,000 units (4 ml) of PAM given in a single injection this has now been adopted for routine use. No differences were observed when the results of different abortive schedules were compared. That dosages lower than those used for curative purposes are adequate is borne out by the experimental work of Eagle, Magnuson & Fleischman [18] and others. While a small quantity of penicillin is sufficient early in the infection, progressively larger doses are necessary later since the treponemes multiply between the time of exposure and the appearance of surface symptoms.

It is difficult in endemic syphilis to determine the exact times of exposure and infection. The time of exposure cannot usually be linked to a definite event as in sporadic venereal syphilis, and a smaller quantity of penicillin may therefore be used in abortive treatment than is necessary to cure the infection, thus masking it or prolonging the incubation period. In order to avoid this danger it is felt that, under the present conditions in Bosnia, the abortive dose should not be reduced below 1,200,000 units of PAM

The criteria for abortive treatment of endemic syphilis differ from those for sporadic venereal syphilis. In endemic syphilis, the first to be considered must be the children since they are the most exposed to infection next, consideration must be given to the mother and child or the husband and wife, if either is suffering from infectious syphilis. Finally the remaining members of the household should be considered, and all members should be treated if any have symptoms of contagious syphilis.

In one family of five, for instance, the initial examination showed that two children had early syphilis with papules in the mouth and on the reproductive organs, and strongly positive serological reactions. The other members of the family were serologically and clinically negative. The infected members of the family were treated with 4,200,000 units of PAM in seven injections, while the others received abortive treatment. Any potential infection in the family was thus taken care of. When the control examinations were carried out 12 and 20 months later no evidence of syphilis was found in the family

An entirely different development took place in another family which is illustrated in fig. 34. Systematic examination of this family revealed that two children (Nos. 1 and 5) had secondary syphilis with strongly positive serological reactions the other children were serologically and clinically

re-treatment. In the three administrative units so far examined (Čehč, Koraj, and Teočak) no new cases of syphilis have been found, while seropositivity has decreased to 2.8 % of the 11,250 inhabitants examined.

If the remaining seropositive cases in this group, the majority of which received re-treatment for reasons of expediency are separated into age-groups, it is significant that only 4.5 % were between 0 and 10 years of age, and 10.1 % between 10 and 20 and that this proportion increased progressively with age, so that more than 66.5 % of seropositive cases were found in the age-group over 40. Thus syphilis morbidity is rapidly decreasing in the lower age-groups while it remains more stationary in the higher although the relative infection-rate in the higher age groups as well is considerably lower than before the campaign started. This augurs well for the future of the long-term control of endemic syphilis in this area.

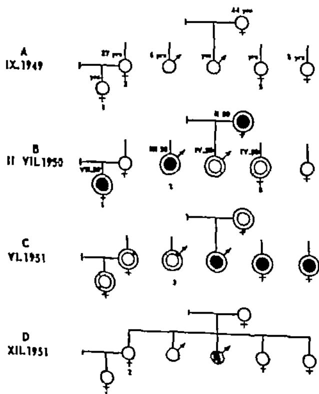
Since the beginning of the campaign, the reservoirs of infection have decreased in most areas in much the same proportions as in the district of Lopare. In the district of Gračanica, however the decrease was less clearly marked, as the original 1948 survey was incomplete and a large number (973) of early syphilis cases were found. However the results have ultimately become fairly satisfactory even in this area. When the first control examination was carried out, it was found that the reservoir of infection had decreased by 71.5 % the second control took place 38 months after the initial examination and, as more thorough work had been done in the interval, particularly in the treatment of contacts, the decrease is now of some 97 %.

It is interesting to note the change during the campaign in the proportion of early syphilis cases to the total number of seropositive cases, representing the decrease in the reservoir of infection. In the district of Gračanica, 42.4 % of infected cases were early syphilitic. At the control examination 18 months later the percentage was 6.3 and 20 months later 2.2. At the beginning of the campaign in Lopare, 6 7 % of the infected population had fresh cases of early syphilis 14 months later these amounted to 1 7 %. As the endemic focus becomes smaller the proportion of early syphilis cases to the total number of infected cases also falls. Although the reduction of the reservoir of infection depends on various factors, the principal one is the abortive treatment of family contacts with PAM At the beginning of the campaign such treatment was only occasionally used as its real value was not appreciated. Later when the first results had been analysed, it became the key to final success. It is now given to all persons whose clinical and serological findings are negative but who are exposed to the risk of infection from other members of the family

In many areas, it is not possible to keep all those who are infected or exposed to infection under observation at frequent intervals over a long period of time. In addition, since primary lesions are rare in endemic syphilis, the question of treatment in the primary seronegative stage rarely

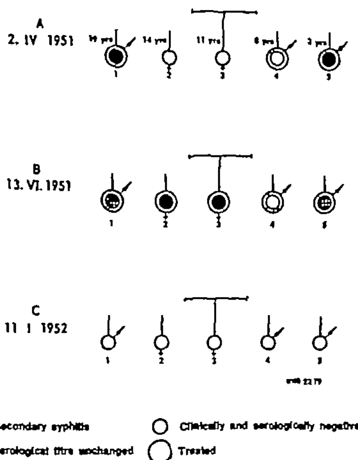
later date. The three infected members of the family were treated, at intervals of one and four months, two others (Nos. 4 and 5) were given abortive treatment, and the remaining child (No. 6) escaped treatment altogether. At the second control examination, it was found that the infected but treated persons were clinically and serologically negative, but that those who either had not been treated or had had abortive treatment had become infected. The entire family was then treated, whether any persons showed symptoms or not, and all but one were clinically and serologically negative six months later: that one, however, showed serological improvement.

FIG. 21. EFFECT OF ABORTIVE TREATMENT (1,200,000 UNITS OF PAM) GIVEN SIMULTANEOUSLY WITH TREATMENT OF INFECTIOUS CASES (VITINICA)



negative. Only one of the apparently uninfected children (No 4) was given abortive treatment the other two did not report for treatment. The entire

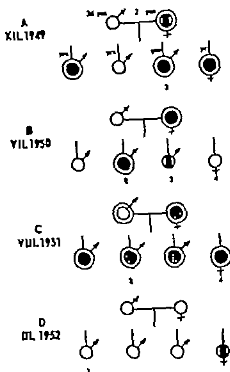
FIG. 34. EFFECT OF ABORTIVE TREATMENT IN A FAMILY WITH A FRESH INFECTION (MHO KRAVICA)



family was urged to present itself for re-examination this it did only two months later On this occasion the two children (Nos. 2 and 3) who had escaped treatment showed fresh clinical manifestations of secondary syphilis with positive serological findings They were given regular PAM treat ment while the others received abortive doses since they could have been reinfected. Another control examination was made eight months later and the entire family was found to be clinically and serologically negative.

The necessity for giving abortive treatment at the same time as infected persons in the family are given the regular treatment is made clear in fig. 35 When the initial examination was carried out, the entire family was clinically and serologically negative but infection was introduced at a

FIG. 36. UNSUCCESSFUL RESULTS WHEN FAMILY CONTACTS REMAIN UNTREATED ([illegible] DRAHOVICA)



Secondary syphilis

Latent syphilis

Clinically and serologically negative

Serological improvement

Serological titre unchanged or increased

Treated ([illegible] units of PAM)

This is illustrated in fig. 36. The initial examination of this family revealed early latent syphilis in the mother while *three* children (Nos. 1 3 and 4) had symptoms of secondary syphilis with strongly positive serological reactions. All the infected members of the family were given the same quantity of PAM.

It is possible that members of a family may escape the disease despite the appearance of fresh infections in their midst, but practical experience has shown that this is not very likely An evaluation of the epidemiological importance of treating contacts was made by a close study of 96 families with a total of 150 children under 10 years of age, since these are they who are considered to be the most exposed to infection in the family and to whom priority should therefore be given in receiving abortive treatment. All were clinically and serologically negative at the initial examination but belonged to families with cases of early infectious syphilis. They were divided into two groups the first included 72 children, each of whom was given 1,200,000 units of PAM at the same time as the infected relatives received regular treatment as a control measure, the second group of 78 children was left untreated. The results, as found in the follow-up examination after six months, are tabulated below

	Treated contacts	*Untreated contacts*	*Total*
Clinically and serologically positive	0	28	28
Clinically and serologically negative	72	50	122
Total	72	78	150

This statistically significant difference between the two groups emphasizes *the epidemiological necessity for the abortive treatment of family* contacts if the chain of infection is to be effectively severed.

During the initial period of the campaign in Bosnia abortive treatment was not given but, once its value had been demonstrated in individual families, it was systematically applied. Its cumulative epidemiological effect is further emphasized by the results in villages and larger areas.

Relapses, Reinfections, and Seroresistance

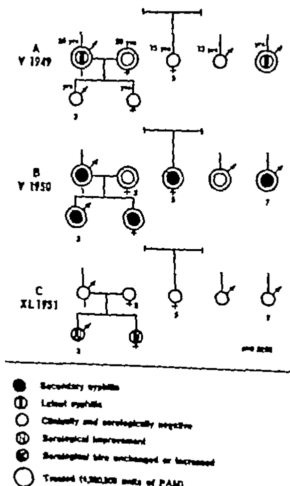
The distinction between true relapses or seroresistance and *reinfection is hardly* possible on clinical or laboratory grounds alone it must be made largely on epidemiological evidence. It is also evident that, since the environmental conditions in which endemic syphilis prevails make the risk of reinfection considerable, it is not possible to evaluate the results of penicillin therapy in series of patients by the cumulative statistical procedure [30] used in sporadic syphilis unless contacts are treated.

It was observed that serological or clinical "relapse" was generally found only in those families in which new infectious cases of syphilis appeared, usually before the "*relapses*" *themselves*. Furthermore, "seroresistance" sometimes observed after regular PAM treatment of early syphilis, was rarely encountered in families where a new infection had not appeared

form of serological improvement but, as a rule, the clinical and serological findings were completely negative.

The importance of treating all possible sources of infection is illustrated in fig. 38. The eldest daughter (No. 3) had been treated in the early latent stage of syphilis with 3,600,000 units of PAM. She was still seropositive 16 months after treatment, and by then had developed clinical manifestations of secondary syphilis with hypertrophic papules in the mouth and on the

FIG. 38. SEROLOGICAL AND CLINICAL RELAPSES IN A FAMILY WITH NEW INFECTIONS (MINO DOBROVCI)

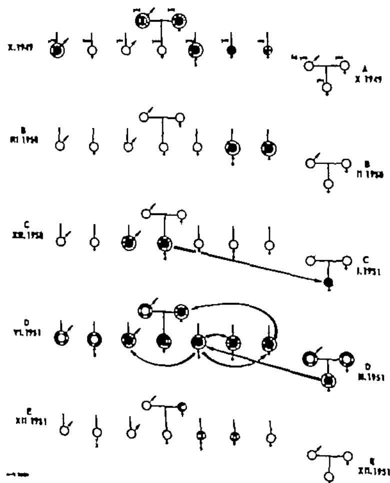


When the first control examination was carried out seven months later the mother had symptoms of secondary syphilis (papules on the tongue and tonsils) with a strongly positive STS titre two of the treated children (Nos. 1 and 4) were clinically and serologically negative and the serological titre in the third child had improved In the meantime, *a fresh infection had appeared* in the 7 year-old boy (No 2) who developed contagious symptoms of secondary syphilis (mucous patches) *before clinical symptoms of secondary* syphilis (" relapse ") appeared in the mother Throughout this time the *father was absent and had no contact with the family* The mother and the infected child once again received the same quantity of PAM but, when the second control examination took place, it was found that the two children (Nos. 1 and 4) who had received treatment and had been serologically and clinically negative at the first control examination had now developed secondary syphilis (clinical " relapse ") So far as the mother and the 7 year-old boy were concerned, the serological findings remained unchanged, while in the younger child (No 3) the titre was found to be higher than before. The explanation can only be that as a reservoir of infection still remained in the family—for the contacts had not been treated—a fresh infection had developed. One might be led to believe that adequate penicillin therapy had no effect on early syphilis and that " seroresistance " remained even a year after treatment. However when the active sources of infection in the family had been completely suppressed by treatment of all the infected members, and abortive treatment had been given to those exposed to the risk of infection and who might be in the incubation period, very satisfactory results were observed seven months later and no further cases of " relapse " or " seroresistance " resulted.

In another case, the initial examination disclosed that two members *of the family (Nos. 1 and 7) had latent syphilis (fig. 37). A year after* treatment with 4,200,000 units of PAM, their serological reactions were strongly positive, *while the younger brother (No 7) had developed* clinical manifestations of secondary syphilis in the form of papules in the oral and anal regions. *These might be interpreted to represent serological* and clinical relapse. Before this happened, however two children, aged 5 and 6 (Nos. 3 and 4) and, *later on, the boy of 15 (No. 5) became infected* —all of them with secondary manifestations. No new infections or " relapses " occurred in this family after regular treatment of all infected members and abortive treatment of family contacts.

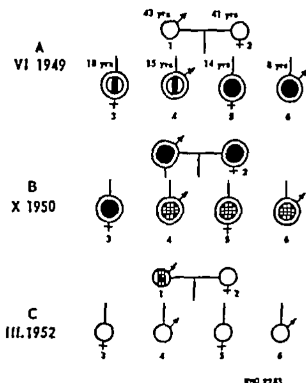
When a control examination disclosed a case of early syphilis 8 to 12 months following treatment with 3 600 000 to 4,200 000 units of PAM or a case where positive serological findings remained unchanged, it was generally found that an infectious case had remained in the family or that a new infection had been introduced. It was observed that there were very few instances in which secondary or early latent syphilis did not respond to PAM therapy within 12 months In a few cases this response took the

FIG. 30. PING-PONG INFECTION AND REINFECTION IN TWO INFECTED FAMILIES AND EPIDEMIOLOGICAL EFFECT OF ABORTIVE TREATMENT ([illegible] SAPKA)



- Secondary syphilis
- Congenital syphilis
- Latent syphilis
- Clinically and serologically negative
- Serological improvement
- Treated (2,400,000 units of PAM; abortive treatment 1,200,000 units)

FIG 33 "SERORESISTANCE" AND CLINICAL "RELAPSE" IN A FAMILY WITH A FRESH FOCUS OF SYPHILIS (WHO TEOCAK)



tonsils. Infection had appeared some months earlier in the father and mother (Nos. 1 and 2), *both of whom became strongly positive after having* been serologically and clinically negative at the first examination The other children (Nos. 4 5 and 6) were also found to have remained serologically positive, no change apparently having occurred 16 months after treatment with PAM The entire family was re treated with the same amount of PAM, and 17 months later they were, with one exception, all clinically and serologically negative.

It was found that relapse or reinfection did not occur in families all of whose members had been treated so long as a fresh infection was not

the results were equally good in families where the few infectious cases and the healthy persons were treated at the same time.

Rose, György & Ingraham,[illegible] Schamberg & Steiger[illegible] and others have advanced the view that, in sporadic venereal syphilis, true relapses are less frequent in children, and that, since they are less exposed to reinfection than adults, better results are obtained from penicillin therapy in children. However since, in endemic syphilis, infection is most frequent in childhood, the same might be expected of reinfection. This, indeed, was found to be the case a comparison of the age-groups of persons suffering from re lapses" after completing PAM treatment shows that approximately 50% of the cases are in children under 10 years of age. The difference in the distribution among age-groups of relapses in endemic and sporadic venereal syphilis must be attributed to the different modes of transmission venereal after the attainment of sexual maturity in sporadic syphilis, and non-venereal in childhood in endemic syphilis.

It may be argued that the response of the human body to penicillin treatment might differ with the age of the infected person and that, in spite of the same treatment, relapses could occur more frequently in some age-groups than in others. However on comparing the effect of identical treatments on the serological titres of persons of different ages, but in whom the duration of the disease was approximately the same, no significant difference was found (fig. 41).

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introduced from outside. To trace the spread of infection from one family to another was often very complicated but fig. 39 does indicate the course of "ping-pong" infection in two neighbouring families. When abortive treatment was given, the infectiousness was eliminated in both.

The influence of residual foci of infection may be seen from three studies made. In the first, of the 240 inhabitants in two villages in the district of Srebrenica, 51 were found to be infected, 40 / of those having early infectious syphilis. Both infected persons and family contacts were treated, and at the control examination eight months later not a single family was found with either a new infection or clinical or serological "relapse"

This is in contrast with the findings in the district of Gračanica, where less systematic work was carried out at the beginning of the campaign. In August 1948, a serological examination of 84 / of the population in an administrative unit with 3 623 inhabitants was carried out 27 / were found to be seropositive, and 135 cases of early infectious syphilis were diagnosed. All infected persons were given a total dose of 4,200,000 units of PAM but no family contacts were treated The follow up examinations took place 22 months later and 53 new cases of secondary syphilis and 7 clinical and 8 serological "relapses" were found. Of the infected cases, 46 / were re-treated and abortive treatment was given to the children of families with fresh cases of syphilis. The percentage of the population which was seropositive remained much the same at 22.4 A second control examination took place 18 months later and 11 new cases of secondary syphilis were found in one small hamlet, in addition to 1 serological and 3 clinical "relapses" The percentage of seropositivity was now found to have fallen to 5 8 /.

A similar situation was also found in a village with 573 inhabitants, 128 of whom had syphilis, 22.6 / with infectious secondary lesions (see fig. 40) During the initial examination, not all the infectious cases were treated nor was abortive treatment given to contacts. At the first control examination 20 months later there was still a large reservoir of infection in the village 23 new cases of secondary syphilis and 4 clinical "relapses" were found. A second control examination four months after the first showed that the new cases of secondary syphilis had been reduced to 3 while one "relapse" had occurred At the third control examination 14 months afterwards, or 39 months after the initial survey no new case of syphilis or instance of "relapse" was found.

On the basis of the observations illustrated above and the findings in other areas, we conclude that the great majority of cases of apparent relapse or seroresistance in early syphilis are actually reinfections. Reduction and elimination of the reservoir produce a corresponding reduction in the number of "relapses" The most successful results were obtained in families all of whose members were infected and to whom treatment was given simultaneously as the family reservoir was thus eliminated at once. But

the results were equally good in families where the few infectious cases and the healthy persons were treated at the same time.

Rose, György & Ingraham,[95] Schamberg & Steiger[96] and others have advanced the view that, in sporadic venereal syphilis, true relapses are less frequent in children, and that, since they are less exposed to reinfection than adults, better results are obtained from penicillin therapy in children. However since, in endemic syphilis, infection is most frequent in childhood, the same might be expected of reinfection. This, indeed, was found to be the case a comparison of the age-groups of persons suffering from re lapses" after completing PAM treatment shows that approximately 50% of the cases are in children under 10 years of age. The difference in the distribution among age-groups of relapses in endemic and sporadic venereal syphilis must be attributed to the different modes of transmission venereal after the attainment of sexual maturity in sporadic syphilis, and non-venereal in childhood in endemic syphilis.

It may be argued that the response of the human body to penicillin treatment might differ with the age of the infected person and that, in spite of the same treatment, relapses could occur more frequently in some age-groups than in others. However on comparing the effect of identical treatments on the serological titres of persons of different ages, but in whom the duration of the disease was approximately the same, no significant difference was found (fig. 41).

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introduced from outside. To trace the spread of infection from one family to another was often very complicated, but fig. 39 does indicate the course of "ping-pong" infection in two neighbouring families. When abortive treatment was given, the infectiousness was eliminated in both.

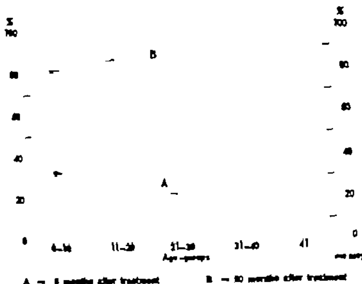
The influence of residual foci of infection may be seen from three studies made. In the first, of the 240 inhabitants in two villages in the district of Srebrenica, 51 were found to be infected, 40% of those having early infectious syphilis. Both infected persons and family contacts were treated, and at the control examination eight months later not a single family was found with either a new infection or clinical or serological "relapse"

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FIG. 41. NEGATIVE CLINICAL AND SEROLOGICAL FINDINGS ACCORDING TO AGE IN [illegible] CASES OF SECONDARY ENDEMIC SYPHILIS 6 AND [illegible] MONTHS AFTER TREATMENT WITH 6 [illegible] UNITS OF PAM



only 70% of the population was examined. The treatment was 3,600 000 units of PAM in six injections. Contacts, however were left untreated and an appreciable reservoir of infection therefore remained. When the first follow-up examination was carried out nearly two years later the situation was more or less unchanged but the team was more careful. The same dose of penicillin was given, and, in many instances, family contacts were also treated. A second follow-up examination four months after the first showed that the infectious cases had decreased to four On this occasion abortive treatment was given to all family contacts. At the third follow-up examination, which took place 39 months after the first survey no new case was found in the village. Infectiousness had been eliminated.

The best and quickest results were obtained when the entire population could be examined during the initial survey and when all infectious cases and family contacts were treated. The achievement in the village of Brusnica may be taken as an example. The entire village of 350 inhabitants was serologically and clinically examined. The infection-rate was found to be 66.6% early infectious syphilis accounting for 48.5% of the cases. The initial examination was carried out in April 1949 when six or seven injections of 600,000 units of PAM each were given to all infected persons in addition, abortive treatment was given to all persons in families with cases of early syphilis. The source of infection was therefore under control.

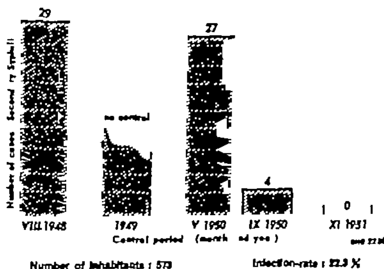
CHAPTER 8

REDUCING THE RESERVOIR OF INFECTION

Owing to technical difficulties and to the shortage of personnel, follow-up examinations could not always be carried out in the Bosnian campaign at the intervals considered most appropriate. On the other hand, this very state of affairs offered an opportunity for a closer epidemiological evaluation of the results from period to period.

In areas with actively expanding foci and numerous fresh infections, the follow up examination should be carried out at a fairly short interval after the initial examination, possibly three to four months afterwards.

FIG. 40. RESULTS AT FOLLOW-UP EXAMINATIONS IN AN ACTIVE FOCUS OF ENDEMIC SYPHILIS (TRNOVCI)



If the interval is too long, the residual cases resulting from persons formerly in the incubation period, or newly imported cases, may under certain *conditions, diminish* the actual effect of the campaign.[34] It is essential that the interval between follow up examinations should not be longer than one year

In the small village of Trnovci (fig. 40) there was an active focus with a relatively high proportion of early infections lesions (29 cases) together with 88 latent and 11 tertiary cases. The initial examination was incompletely carried out owing to the limited experience of the team at the time

Epidemiological incidents of this kind will always occur and show clearly that further supervision is necessary after organized field campaigns in local areas have come to an end.

It is interesting to consider the general results achieved in an infected area up to the time when it ceases to require a specially organized field campaign. The gradual decline in the seropositivity and in the number of early infectious cases in the administrative unit of Sapna, from the start of the campaign to the last control examination 27 months later is shown in fig. 43.

The first follow-up examination took place six months after the initial survey during which the 136 infectious cases found had been treated with 4,200,000 units of PAM each. During this period the seropositivity-rate had decreased by nearly half, and the reservoir of infection, by 87.5 %. Treatment with the same dosage was repeated in 24.2% of the initial cases.

The second control examination was made 21 months after the initial survey and it was discovered that seropositivity had decreased to 5.7%, a figure which includes both doubtful and positive reactions. The reservoir of infection, however was only slightly reduced as abortive treatment had not been given. In the village of Medjedja, an old endemic focus, a fairly high percentage of treated cases remained seropositive even after re-treatment. The majority of these were late latent cases and were treated for the third time with a larger dose of PAM, 7,200,000 units being given in three injections. Fresh cases of syphilis were given the same treatment as at previous examinations, and abortive treatment (1,200,000 units) was given to all exposed members of families with fresh syphilis.

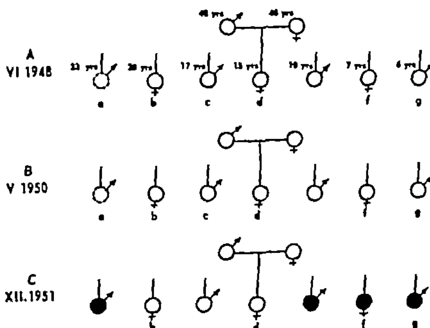
At the third control examination, 27 months after the campaign had started, it was found that the seropositivity had fallen to 1.4 % and that the reservoir of infection had been eliminated.

Improvement of living conditions and general hygiene will lessen the risk of spreading endemic syphilis when cases reappear. Although social and economic betterment plans are under way it is likely that a general improvement in Bosnia will take time and the point has not been reached where the reintroduction, and further non-venereal transmission, of infection within and among families can be completely eliminated. But the risk that this will result in widespread infection of the population is greatly reduced by the epidemiological effect of the mass-treatment campaign. The reservoir as a whole has been brought under control, and the attitude of the people to the problem has been altered this is due partly to some general improvement in social and economic conditions, partly to the work of the field teams and to the general progress of the campaign, and partly to the fact that new cases of endemic syphilis are now detected more rapidly and can be more quickly dealt with.

Since then, five follow up examinations have been carried out. At the fourth, held at the beginning of 1951 only one young man, who had previously been absent from the village, was found to have a fresh case of syphilis he was treated. At the last examination (April 1951), three years after the start of the campaign, the village was free from infection. There were no new cases of syphilis, and only four inhabitants remained seropositive. Of those, two had doubtful reactions and two positive, one of whom was a woman of 63 whose serological findings remained strongly positive despite three courses of treatment with PAM she had no clinical manifestations.

However such success could not always be counted on. Single instances of fresh infection were sometimes encountered after the second control examination, but they were usually found to be confined within limited areas and to recur in a small number of families. Such reintroduction of the disease by a member of a family who had been absent during the campaign and had been neither examined nor treated is illustrated in fig. 42.

FIG. 42. INFECTION OF FAMILY BY RETURN OF ABSENT MEMBER (MNO MOLESICI)



Epidemiological incidents of this kind will always occur and show clearly that further supervision is necessary after organized field campaigns in local areas have come to an end.

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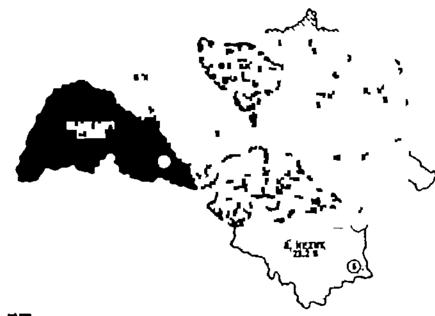
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FIG. 42. SEROPOSITIVITY RATE AND NUMBER OF CASES OF SECONDARY SYPHILIS (MNO SAPNA)

Systematic Examination and Treatment—2.X.1949 Seropositive: 21.3 %



First Control Examination—4.IV 1950 Seropositive: 13.7 %



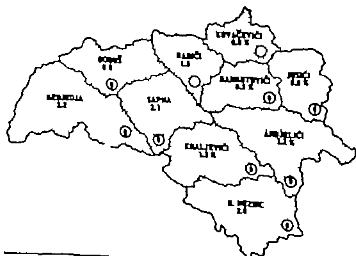
○ Number of cases of secondary syphilis

FIG. [illegible]. SEROPOSITIVITY-RATE AND NUMBER OF CASES OF SECONDARY SYPHILIS (DIMO SAPNA) (continued)

Second Control Examination—[illegible] Seropositive : 1.7 %



Third Control Examination—[illegible] Seropositive : 1.4 %



○ Number of cases of secondary syphilis

In our experience it is possible under favourable conditions, and in limited areas, to eradicate the infectious reservoir completely within a short period of time by mass treatment. In other cases, the disease can be checked and the infectious reservoir reduced to a minimum over a somewhat longer period and ultimately eliminated. In both instances true relapses and reinfections, and reintroduction of the disease from other areas, must be watched for The epidemiological situation cannot conceivably return to its original form after one or two follow up examinations have been made, but constant supervision of previously endemic areas is necessary as part of the long-term programme. In Bosnia, such supervision and health control are provided by one or more health workers remaining in the field between control examinations and after the field campaign proper has come to an end. Being selected from the field teams, they are familiar with endemic syphilis as a rural health problem in all its aspects. This system has already proved invaluable in achieving lasting results. The health workers co-operate with the local health centres, which assume the responsibility for keeping the disease under control through their normal machinery against communicable diseases, in the "consolidation phase"[83] of the long-term programme.

The present programme is serving as a bridgehead to the development of general public health services and to the expansion of the machinery against communicable diseases as advantage is taken of the advances already made the population has been made aware of the need for such services, and its numbers are known staff has been recruited the basis of a sound record system has been established and, in many communities, facilities have already been set up or existing ones expanded.

SUMMARY

Historical evidence indicates that it is likely that syphilis was introduced into Bosnia from different countries at different periods of time, with the Ottoman armies playing the major role in its spread. By the end of the 19th century it was already widespread in Bosnia and Herzegovina and records for 1905-11 show that, in investigations carried out in 37 districts, 41,398 clinical cases were found—an infection-rate of 8.3%. Studies made from 1926 to 1933, at which time serological examinations were carried out, revealed 57,965 cases, or an infection-rate of 11.8% of the population examined.

Since 1948, the Yugoslav health administration has developed a nationwide syphilis-control programme, with special effort to control the non-venereal endemic syphilis in Bosnia. The World Health Organization and the United Nations International Children's Emergency Fund have participated at the request of the Yugoslav Government. For a number of reasons, all previous control efforts had been unsuccessful, principally because no systematic examination of the entire population had been attempted and because stress had been laid on the clinical and pathological rather than on the epidemiological aspects of the disease.

Discussing the concept of endemic syphilis, the author gives the following as the essential characteristics of the disease:

(1) It is generally not venereally transmitted and is not considered as a venereal disease by the affected population, it is most frequently acquired in childhood.

(2) It is prevalent in areas where a low standard of education and poor economic

RÉSUMÉ

L'histoire nous enseigne que la syphilis a été vraisemblablement importée en Bosnie de différents pays, à diverses époques et que ce sont les armées ottomanes qui ont le plus contribué à la propager. Cette maladie était déjà très répandue en Bosnie-Herzégovine vers la fin du XIXe siècle. D'après les statistiques des années 1905 à 1911 41.398 cas cliniques ont été décelés au cours des enquêtes menées dans 37 districts, soit un taux d'infection de 8,3%. Les séro-réactions pratiquées de 1926 à 1933 ont révélé 57.965 cas, soit un taux d'infection de 11,8% pour la population examinée.

L'administration yougoslave a entrepris depuis 1948 une vaste campagne antisyphilitique dans l'ensemble du pays, en s'efforçant tout particulièrement de combattre la syphilis endémique d'origine non-vénérienne qui sévit en Bosnie. A la demande du Gouvernement yougoslave, l'Organisation Mondiale de la Santé et le Fonds International des Nations Unies pour le Secours à l'Enfance ont participé à ces efforts. Toutes les campagnes antérieures étaient demeurées inefficaces pour diverses raisons, mais surtout parce que le dépistage n'avait pas été étendu systématiquement à l'ensemble de la population et qu'on ne s'était attaché aux aspects cliniques et pathologiques de la maladie plutôt qu'à son épidémiologie.

Examinant la notion de syphilis endémique, l'auteur décrit comme suit les caractéristiques essentielles de cette maladie

1. En général, elle n'est pas transmise par voie génitale et n'est pas considérée par la population atteinte comme une maladie vénérienne. La plupart du temps, l'infection est contractée au cours de l'enfance.

2. Elle est répandue dans des régions où le niveau de l'instruction est bas et les

and social conditions, with primitive sanitary and dwelling arrangements, are general.

(3) Its *particular* mode of spread, through common domestic and household *utensils, and other direct and indirect* contacts, often results in the appearance of infectious lesions in the oral region as *the first* symptom.

(4) There are no essential differences between the clinical picture of endemic *syphilis and that of sporadic* venereal syphilis.

Syphilis in Bosnia must be seen as an epidemiological rather than a clinical problem. It became endemic because of the existence over centuries of epidemiological features favouring a distinct non-venereal mode of spread. It is mainly found among the rural population, but it is unevenly *distributed over different* areas, or even within an area, despite apparently identical living conditions. This uneven distribution may be explained by a variety of factors, including social and *family customs, population* movements, topography and poor communications.

There is ample evidence that close family links and social contacts constitute an important factor in facilitating the spread of endemic syphilis. A study of prevalence in relation to the size of the community shows that the smaller and more compact the community the higher the infection-rate, as there are more *opportunities* for transmission of *Treponema pallidum*. It was also found that, wherever there was a high proportion of infected children, syphilis was more active and the endemic spreading while, where that proportion was low the disease was less active and the endemic waning. At the same time, it was observed that the infection-rate among children varied considerably according to the number of *parents* infected and one study of 642

conditions économiques et sociales défavorables, et dont la population vit dans des logements primitifs pourvus d'installations sanitaires rudimentaires.

3 En raison de son mode particulier de propagation par l'intermédiaire d objets domestiques usuels et d ustensiles de ménage, ou par d'autres contacts *directs* ou indirects, le premier symptôme consiste fréquemment en des lésions infectieuses de la région buccale.

4 Il n existe pas de différences importantes entre le tableau clinique de la syphilis endémique et celui de la syphilis sporadique d origine vénérienne.

En Bosnie, la syphilis doit être considérée comme posant un problème épidémiologique plutôt que clinique. Elle est devenue endémique par suite de l existence séculaire de facteurs épidémiologiques de nature à favoriser un mode particulier de transmission non vénérienne elle est *répandue principalement dans* la population rurale, mais n est pas répartie également dans les différentes zones, si bien que sa *fréquence* peut, malgré l'identité apparente des conditions de vie, varier à l'intérieur *d'une seule et même région*. Cette répartition irrégulière de la maladie peut s expliquer par diverses causes, notamment par les habitudes familiales et sociales, les migrations intérieures, la topographie et l *insuffisance des voies de communication*.

Il y a de nombreuses raisons d admettre que la *promiscuité* de la vie familiale et l étroitesse des relations sociales constituent un facteur important dans la propagation de la syphilis endémique. Une étude concernant l'influence que l'importance numérique d'une collectivité peut exercer sur le taux de fréquence de la maladie a permis d établir que ce taux est d autant plus élevé que la collectivité est moins nombreuse et sa vie plus resserrée, ce qui accroît les risques de transmission de *Treponema pallidum*. Il a été constaté, d autre part, que la syphilis est plus active et d une endémicité croissante dans les régions où une grande proportion des enfants sont *infectés Inversement*, elle est moins active et son endémicité tend à décroître là où la proportion

infected families showed that in 20% of them the children alone were infected.

Endemic syphilis was long thought to be benign disease, partly in consequence of the attitude to it of the patients living in primitive conditions. The symptomatology of both endemic syphilis and sporadic venereal syphilis is similar and treatment with specific drugs has a similar influence in both diseases the difference is rather in the natural course of the disease and in the attitude of the patients. Since endemic syphilis is chronic infectious disease hich rarely causes death or produces total incapacity for work, it is not considered by the population mainly affected to be so grave as it is by those who live under more developed conditions. However in regions here there has been gradual improvement in the conditions of the rural population, manifestations of syphilis are now considered as a burden and an obstacle to economic and social advancement.

Primary lesions are rare in endemic syphilis, systematic examinations of large groups showing them to occur in less than 1 / of the early cases. Their occurrence depends largely on the conditions under hich the infection was contracted and on the size of the inoculum. In the Bosnian environment, treponemes are generally non-venereally transmitted in small numbers occasional transmission of large numbers does occur however, and may result in primary lesions. This is, for instance, the case when *primary lesions* of the mother's nipple are found. The long-lasting direct contact in breast feeding facilitates the entry of great numbers of treponemes from the oral mucosal lesions in the child.

d'enfants infectés est plus faible. Il a été observé, d'autre part, que le taux d'infection des enfants varie considérablement selon le nombre de parents contaminés. Il ressort ainsi d'une étude qui porté sur 642 familles infectées que dans 20 / d'entre elles, seuls les enfants étaient atteints.

On a longtemps considéré la syphilis endémique comme une maladie bénigne, ce qui s'explique en partie par l'attitude des malades vivant dans un milieu primitif. La symptomatologie de la syphilis endémique ne diffère guère de celle de la syphilis sporadique d origine vénérienne, et le traitement par les remèdes spécifiques influe de façon analogue sur ces deux tréponématoses. La différence réside plutôt dans leur évolution naturelle et dans l'attitude des malades. Comme la syphilis endémique est une maladie infectieuse chronique qui 'est que rarement mortelle et entraîne qu'exceptionnellement une invalidité totale, les habitants ne lui reconnaissent pas le caractère de gravité qu'elle revêt aux yeux de populations plus évoluées. Toutefois, dans les régions rurales où les conditions de vie se sont progressivement améliorées, les manifestations de la syphilis sont considérées actuellement comme une lourde charge de nature à entraver le développement économique et social.

Les lésions primaires sont rares dans la syphilis endémique· Il ressort d examens systématiques de groupes importants de population que leur fréquence est inférieure à 1% dans les infections récentes. Leur apparition dépend surtout des conditions dans lesquelles l infection a été contractée, ainsi que de la quantité des germes inoculés. Dans la population bosniaque, les tréponèmes sont généralement transmis par voie non-vénérienne et en nombre restreint Il arrive, toutefois, qu'ils soient plus nombreux et ils provoquent alors des lésions primaires. C'est ainsi que expliquent, par exemple, les lésions primaires du mamelon observées parfois chez les mères le contact direct et prolongé amené par l'allaitement facilite en effet l'entrée dans l organisme maternel d'un grand nombre de tréponèmes provenant des lésions des muqueuses de la région buccale de l'enfant.

Late manifestations are similar to those of sporadic venereal syphilis, with gummatous lesions on the skin, in the naso-pharyngeal region, and in the osteo-articular system. Contrary to previous belief, field investigations have shown that involvement of the central nervous system also occurs.

Superinfection of an already infected and allergic host is considered to be the chief reason for the frequency of tertiary lesions. When living conditions improve and the chances for non-venereal transmission decrease, or when infectious cases are treated, the number of active tertiary *lesions diminishes in endemic areas. Thus* their frequency represents an epidemiological index of the state of activity of rural endemic foci.

It was previously thought that the non-occurrence of congenital manifestations was one of the characteristics of endemic *syphilis. However though rare, they do* occur Their rarity is largely due to the *fact that, as infectiousness in syphilis* decreases *with* time and since in endemic syphilis many years generally elapse between the acquisition of the infection and the attainment of maturity there *is little* probability of a mother's giving birth to a congenitally syphilitic child.

One section of this paper deals with the *organization of the field campaign,* emphasizing that case-finding was done by systematic serological screening of the *entire population in addition to clinical* investigation, and that follow-up examinations included re-examining not only treated cases but the remainder of the susceptible population as well. In all, approximately 95 % of the total census population in endemic areas was examined and 35,238 cases, or 8.1 % of the examined population, were treated.

As the highest infection-rate was found in north-eastern Bosnia, the most intensive field-work was done in that area and

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La surinfection de sujets déjà infectés et allergiques est considérée comme la principale cause de la fréquence des lésions tertiaires. Lorsque, parallèlement à l'amélioration des conditions de vie, les risques de transmission non-vénérienne diminuent, et que les malades contagieux sont traités, *les lésions tertiaires actives deviennent plus* rares dans les zones d endémicité leur taux de fréquence peut donc être censé représenter *l'indice épidémiologique de l activité* des foyers endémiques en milieu rural.

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The distinction between true relapses or seroresistance and reinfection is hardly possible on clinical or laboratory grounds alone It must be made largely on epidemiological evidence. It was observed that apparent cases of clinical or serological relapse or seroresistance were generally found only in those families in which fresh cases of syphilis appeared and where not all the members with early syphilis had been treated. It was therefore evident *that the great majority of relapses, or* so-called seroresistant cases of early syphilis, were, in fact, reinfections.

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Il n'est guère possible, en se fondant exclusivement sur des constatations cliniques ou sérologiques, de distinguer les vraies rechutes ou cas de séro-résistance des réinfections Il convient donc de faire largement appel, à cet effet, aux données épidémiologiques. Il a été observé que les cas apparents de rechute clinique ou sérologique ou de séro-résistance survenaient uniquement dans les familles où de nouvelles infections syphilitiques s'étaient *déclarées et dont tous les membres atteints* de syphilis récente n'avaient pas été soumis au traitement. Il est donc apparu que la grande *majorité des rechutes ou les cas* de syphilis récente, réputés séro-résistants, étaient, en fait, des réinfections.

On a estimé que la réduction du réservoir de l'infection dépendait dans une large mesure de l'administration d'un traitement abortif aux contacts familiaux. Toutes les personnes dont l'examen clinique et sérologique s'était révélé négatif et qui risquaient d'être contaminées par d'autres membres de leur famille ont été soumises *à un traitement de ce genre. Après* l'essai de doses diverses, on a finalement adopté, dans ce cas, une posologie de 1.200.000 *unités de PAM, administrées en une seule* injection.

L'auteur est d'avis qu'il est possible, par un traitement en série, de tarir complètement et rapidement le réservoir de l'infection dans des zones limitées et présentant des conditions favorables. Lorsque les conditions sont moins favorables, la maladie peut être enrayée et le réservoir réduit au minimum au bout d'une période plus longue, si bien qu'en définitive, il est possible de supprimer radicalement la syphilis endémique.

En conclusion, l'auteur indique que le *programme* de lutte contre la syphilis endémique en Bosnie doit permettre d'amorcer l'organisation de services généraux de santé publique, qui seront créés à mesure que les résultats acquis auront été

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Il n'est guère possible, en se fondant exclusivement sur des constatations cliniques ou sérologiques, de distinguer les vraies rechutes ou cas de séro-résistance des réinfections Il convient donc de faire largement appel, à cet effet, aux données épidémiologiques. Il a *été* observé que les cas apparents de rechute clinique ou sérologique *ou de séro-résistance survenaient* uniquement dans les familles où de nouvelles infections syphilitiques s'étaient *déclarées et dont tous les membres atteints* de syphilis récente n'avaient pas été soumis au traitement. Il est donc apparu que la grande *majorité* des rechutes ou *les* cas de syphilis récente, *réputés* séro-résistants, étaient, en fait, des réinfections.

On a estimé que la réduction du réservoir de l'infection dépendait dans une large mesure de l administration d'un traitement abortif aux contacts familiaux. Toutes les personnes dont l examen clinique et *sérologique s'était révélé* négatif et qui risquaient d être contaminées par d autres membres de leur famille ont *été* soumises *à un traitement de ce genre. Après l* essai de doses diverses, on a finalement adopté, dans ce cas, une posologie de 1.200.000 *unités de PAM, administrées en une seule* injection.

L'auteur est d'avis qu'il est possible, par un traitement en série, de tarir complètement et rapidement le réservoir de l'infec tion dans des zones limitées et présentant des conditions favorables. Lorsque les conditions sont moins favorables, *la maladie* peut être enrayée et le réservoir réduit au minimum au bout d'une période plus longue, si bien qu en définitive, il est possible de supprimer radicalement la syphilis endémique.

En conclusion, l auteur indique que le *programme de lutte contre la syphilis* endémique en Bosnie doit permettre d amorcer l organisation de services généraux de santé publique, qui seront créés à mesure que les résultats acquis auront été

ANNEX

STUDIES ON TREPONEMES FROM CASES OF ENDEMIC SYPHILIS

THOMAS B. TURNER, M.D.

DAVID H. HOLLANDER, M.D.[a]

Introduction

In 1950 the World Health Organization made a grant to Johns Hopkins University for the establishment of an International Treponematosis Laboratory Center The purpose of the centre was to study in collaboration with field teams and other laboratories, certain problems which appeared to be basic to a long-range worldwide attack on the treponematoses. One of these problems was conceived to be an elucidation of the biological relationship between species and strains of treponemes isolated from different clinical syndromes as they existed in various parts of the world.

Among the first of such syndromes selected by this laboratory for investigation was endemic syphilis, which was then under extensive field study in Yugoslavia by Dr E. L Grin and his associates, with the support of WHO In collaboration with Dr Grin, two strains of treponemes from patients in Bosnia were successfully established in laboratory animals and subjected to further study in this laboratory

Isolation of Strains

For the attempted isolation of strains, rabbits and hamsters were shipped by air from Baltimore to Sarajevo. The transfer of human material to animals was made by Dr Grin, and the animals were returned promptly by air to Baltimore, where they were subsequently observed by the writers.

Transfers were made from three patients on 5 September 1950, with successful isolations in two instances. These two strains of treponemes have been designated as Bosnia A and Bosnia B

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Character of the Lesions Induced in Rabbits

The Bosnia A and Bosnia B strains behaved so much alike in laboratory animals that the statements made here will apply to both unless otherwise indicated. Comparisons will be made with nine recently isolated strains of treponemes, as well as with the Nichols strain of *Treponema pallidum* which has been so widely used in laboratory studies. Among the recently isolated strains, three were isolated from patients with venereally acquired syphilis Chicago, Baghdad A, and Baghdad B three from patients with bejel Syria A, Syria B, and Iraq B and three from patients with yaws Haiti A, Haiti B, and Indonesia B.

The Bosnia A strain has now been through 19 animal passages in rabbits. Of 38 animals inoculated intratesticularly lesions in which *T pallidum* has been demonstrated developed in 37 The Bosnia B strain has also been through 19 passages in rabbits at the time of writing, with positively identified lesions in 40 of 42 animals inoculated intratesticularly Twelve rabbits have been inoculated intradermally with the Bosnia A strain in four it was the sole method of inoculation in the other eight, it was combined with testicular inoculation. Twelve rabbits have also been inoculated intradermally with the Bosnia B strain in four of these animals this was the sole method of inoculation.

Detailed comparative data on these strains will be published elsewhere. Suffice it to say here that the main difference between all these strains is in their capacity to produce indurated lesions in rabbits. This, in turn, appears to be related to the production, presumably by the treponemes, of a mucoid material which has been identified as hyaluronic acid. A study of histopathological material from rabbit lesions shows no significant qualitative difference between the Bosnia strains and other syphilis strains. Quantitatively however less metachromatic staining mucoid material is, *in general*, observed than with the other syphilis strains, but much more than with the yaws strains. The hypothesis has been advanced [7] that the principal difference in the reaction of the rabbit to the treponemal group of organisms resides in the production of hyaluronic acid. This difference may lie either in the amount of mucopolysaccharide produced, or in an actual chemical difference in the hyaluronic acids produced by different strains and species and a difference in the susceptibility of these products to the enzymes of the rabbit which are concerned with the disposal of hyaluronic acid.

Using as a criterion the extent to which mucoid material is present and indurated lesions are produced, both the Bosnia strains conform more to the pattern of that exhibited by rabbits inoculated with strains of venereally acquired syphilis—the Nichols, Chicago, Baghdad A, and Baghdad B strains—than they do to that induced by the strains of yaws treponemes under study Indurated lesions of a type commonly encountered in syphilis

Bosnia A strain

The patient from whom this strain was obtained was a 35-year-old man, K. A S., *History No 86/50* *According to Dr Grin s notes*, the patient had mucous patches under the tongue and on the tonsils papular secondary lesions on the face trunk, and extremities, with some becoming pustular and moist condylomata on the genitalia. Kahn and Meinicke serological reactions were positive.

The material for inoculation of animals was collected, in a mixture of serum and saline from an ulcer on the shaft of the penis darkfield examination of this material showed many treponemes. One rabbit was inoculated as follows 0.5 ml was injected into the body of each testis, and 0.1 ml intradermally at each of four sites on the clipped back. One hamster was given intradermal inoculations in each side of the scrotum and at four sites on the back, the amount injected at each site being approximately 0.2 ml.

The animals arrived in Baltimore in good condition On the 70th day after inoculation slight changes were noted in each epididymis of the rabbit and, upon excision of the testis, typical motile treponemes were demonstrated. This material was transferred to the testes of two normal rabbits, which developed lesions in about 30 days. This strain has now been through *19* successive animal passages. No evidence of infection developed in the hamster inoculated directly from the patient, although the lymph nodes of the hamster were not examined.

Bosnia B strain

The patient from whom this strain was obtained was a 38 year-old man, N G G History No 19/50 Four other members of his family—his wife and three children—were also infected. Examination of the patient revealed mucous patches in the mouth and moist condylomata lata on the skin of the scrotum. Material collected from the latter lesions in serum saline showed treponemes on darkfield examination. The Kahn and Meinicke tests were positive.

One rabbit was inoculated as follows 0.4 ml into the body of each *testis and 0 1 ml intradermally at four sites on the clipped back.* The animal arrived back in Baltimore in good condition On the 76th day after inoculation lesions were noted in the testes, and on excision each showed enlargement of the head of the epididymis and pinpoint lesions on the surface of the testis. Transfers were made to two other rabbits, which developed testicular and cutaneous lesions in 21 days. This strain also has now been through 19 successive animal passages.

Bosnia C strain

Material was transferred to two hamsters only Since the strain was not recovered from these animals, no further details will be given.

Immunological Relationship

The immunological relationships between the newly isolated strains and the Nichols strain which was isolated in North America in 1911 were examined by a series of challenge inoculations. Rabbits were inoculated intratesticularly with the Nichols strain of *T. pallidum* and the animals allowed to progress through the usual evolution of the disease. Between three and four months after the original inoculation, at a time when the animals were known to be immune to the homologous strain, groups of four of these rabbits, together with four normal rabbits as controls, were inoculated intradermally on the back with the challenge strain. Failure of lesions to develop in the previously infected rabbits, when characteristic lesions developed in the controls, was regarded as evidence of a substantial degree of cross-immunity between the two strains.

Employing the foregoing experimental method, the following results were obtained of four animals previously infected with the Nichols strain, none developed lesions upon challenge with 5 000 treponemes of the Bosnia A strain injected into each of four sites, whereas four control animals similarly inoculated developed a characteristic pattern of lesions. The same results were obtained when a group of four rabbits immune to the Nichols strain was similarly inoculated with the Bosnia B strain, together with four normal controls.

It is concluded on the basis of the foregoing evidence that both of the Bosnia strains are closely related immunologically to the Nichols strain. Since numerous other syphilis strains have also been shown to bear a similar relationship to the Nichols strain [8] it is concluded that the Bosnia strains behave, in this respect, like most other syphilis strains isolated in various parts of the world, but more particularly in North America.

Penicillin Sensitivity of Bosnia Strains

Laboratory studies on the sensitivity of a particular strain of treponemes cannot be interpreted directly in terms of treatment of the clinical disease in patients. Nevertheless, laboratory data of a comparative nature can be very useful when viewed in the light of clinical experience with one or another of the treponematoses. The Bosnia strains have been subjected to laboratory study with this point in mind.

The penicillin sensitivity of these strains was tested by in vivo and in vitro methods. The former is a relatively crude method devised in this laboratory [9] and has been used for screening purposes only. Using the Nichols strain as a standard of reference, it has been determined that the Bosnia strains when tested in either rabbits or hamsters respond in essentially the same manner as the reference strain and the other newly isolated syphilis strains.

were observed in the first two or three passages and, while not all the inoculated animals have shown these typical lesions in subsequent passages, the Bosnia strains unquestionably have the capacity to induce syphilis-like lesions in the rabbit.

Character and Frequency of Lesions in Hamsters

Some years ago Bessemans and de Moor [1] noted that, when the golden or Syrian hamster (*Mesocricetus auratus*) was inoculated with *T pallidum*, lesions ordinarily did not develop but the animal acquired a symptomless infection as manifested by the presence of readily demonstrable treponemes in the lymph-nodes. More recently Geiman [8] has reported that lesions can be produced in hamsters by yaws treponemes but not usually by syphilis strains.

In our hands each of the 12 newly isolated strains has at one time or another produced specific, local ulcerated lesions in hamsters after intradermal inoculation in the groin or scrotum or into the tissues of the lip. These lesions do not differ significantly in character according to the species of treponemes inoculated but, from our experience as a whole, it may be said that the yaws and bejel treponemes have produced lesions in a higher proportion of the hamsters inoculated than have the new syphilis strains. Moreover most of the hamsters which have developed very extensive lesions have been inoculated with either yaws or bejel treponemes. Since a number of factors, such as the temperature of the environment and the size of the inoculum have not been adequately controlled it cannot be said at this time that there is a real difference in the behaviour of this animal species to different strains of treponemes. Almost without exception, however motile treponemes can be demonstrated in the lymph-nodes of hamsters inoculated with syphilis as well as with yaws and bejel treponemes.

It is of interest, however that, unlike the lesions induced in rabbits by *T pallidum*, the lesions in hamsters exhibit little, if any induration, although they are customarily swarming with treponemes. What may be the biological basis of this variation in the response of these two animal species to the same strain of *T pallidum* is not known again, it is possible that the hyaluronic acid/hyaluronidase system may be involved.

Of eight hamsters inoculated with the Bosnia A strain, five developed external darkfield-positive lesions, and treponemes were demonstrated by darkfield examination of the inguinal nodes of the other three. The Bosnia B strain produced lesions in five of seven hamsters inoculated, and each of the other two animals showed motile treponemes upon darkfield examination of the inguinal lymph-nodes. These results are cited as a matter of interest only since no conclusions of a comparative nature can be drawn from them

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strains and reference strain of *T. pallidum* (the Nichols strain) to which numerous other strains of the same treponeme have been shown to be similarly related. Strains of treponemes isolated from some patients suffering from bejel or yaws have also shown this same close immunological relationship.

The Bosnia strains demonstrated the same order of sensitivity to penicillin as the Nichols strain and other recently isolated strains of syphilis, bejel, or yaws treponemes.

The authors conclude that the Bosnia A and Bosnia B strains belong to the general group of strains commonly designated *T. pallidum* and that the response to therapy of patients with endemic syphilis should follow much the same pattern as that observed in patients with venereally acquired syphilis.

Bosnie et une souche de référence de *T. pallidum* (souche Nichols), dont la parenté avec de nombreuses autres souches du même tréponème a été également prouvée. Des souches de tréponèmes isolées de quelques malades atteints de béjel ou de pian ont montré la même étroite relation.

Les souches de Bosnie présentent une sensibilité à la pénicilline analogue à celle de la souche Nichols et d'autres souches récemment isolées de tréponèmes de la syphilis, du béjel ou du pian.

Les auteurs concluent que les souches Bosnie A et Bosnie B appartiennent au groupe général communément désigné comme *T. pallidum* et que l'effet du traitement devrait être à peu près le même chez les malades atteints de syphilis endémique que chez les malades souffrant de syphilis vénérienne.

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A more sensitive index of penicillin effects is provided by the in vitro methods developed and applied by our associate Miss Ellen Nell. These methods are essentially those employed in testing other organisms by the dilution method, with special adaptations to the more difficult problem of assay against the treponemal group of organisms, as described elsewhere.[3]

Again employing the Nichols strain for reference, it has been found that the amount of penicillin which will render 50 / of the treponemes non-motile in 18 hours, using control tubes for purposes of comparison, is of the order of 0 0019 μ per ml of test material. The corresponding figure for Bosnia A is 0 0013 and for Bosnia B, 0 0012, both of which are well within the limits of variation of the method. It is of interest, too that all other strains tested fell within these general limits.

It seems fair to conclude, therefore, that the Bosnia strains of endemic syphilis do not vary significantly in their penicillin sensitivity from other strains of treponemes isolated in other parts of the world and from various clinical syndromes. These results suggest that types of penicillin treatment which are found to be effective in other treponemal diseases will be equally effective in the endemic syphilis of Bosnia. Should significant clinical differences be noted between the reaction of the host in endemic syphilis and that commonly observed in venereally acquired syphilis, it appears that they may best be explained by epidemiological or sociological factors rather than by important biological differences in the infecting treponemes.

SUMMARY

Two strains of treponemes, designated "Bosnia A and Bosnia B" were established in laboratory animals which were flown from Sarajevo Yugoslavia, to Baltimore, Md., USA, where their biological relationship to strains isolated from other clinical syndromes appearing in various parts of the world was studied at the International Treponematosis Laboratory Center Both strains went through 19 successive animal passages in rabbits, and it was found that they resembled each other in all the characteristics noted in the laboratory Moreover the disease picture which the strains produced in rabbits and hamsters had many characteristics in common with that produced by other strains of *Treponema pallidum* in North America and elsewhere.

A close immunological relationship was also demonstrated between the Bosnia

RÉSUMÉ

Deux souches de tréponèmes, dénommées « Bosnie A » et « Bosnie B », ont été inoculées à des animaux de laboratoire qui ont été envoyés par avion de Sarajevo (Yougoslavie) à Baltimore, Md. (Etats-Unis d Amérique). Les auteurs ont étudié, au Laboratoire central international des Tréponématoses, la relation biologique existant entre ces souches et celles qui avaient été isolées d autres syndromes dans différentes parties du monde. Après 19 passages successifs sur le lapin, toutes les caractéristiques de ces souches observées au laboratoire se sont avérées identiques. En outre, les manifestations pathologiques déterminées par ces deux souches chez le lapin et le hamster présentent de nombreux traits communs avec celles qui ont été produites par d autres souches de *Treponema pallidum* en Amérique du Nord et ailleurs.

Une relation immunologique étroite a pu être démontrée entre les souches de

strains and reference strain of *T. pallidum* (the Nichols strain) to which numerous other strains of the same treponeme have been shown to be similarly related. Strains of treponemes isolated from some patients suffering from bejel or yaws have also shown this same close immunological relationship.

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